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ANNALS
OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

ANNALS OF HEAD & NECK MEDICINE & SURGERY

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PREDICTING RADIORESISTANCE IN EARLY GLOTTIC SQUAMOUS CELL CARCINOMA BY DNA CONTENT

RECURRENT PAROTITIS AND SIALECTASIS IN CHILDHOOD

NDOSCOPIC SURGERY OF THE VIDIAN NERVE

OXIC SHOCK SYNDROME ASSOCIATED WITH PHARYNGITIS AND SUBMANDIBULAR SPACE ABSCESS

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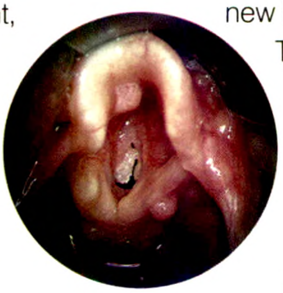

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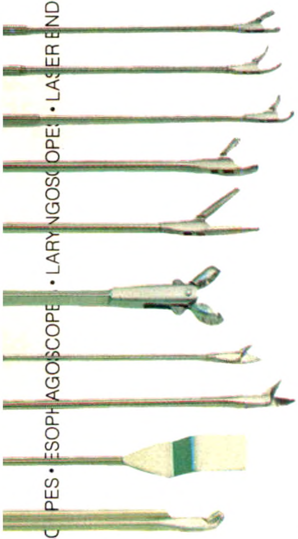

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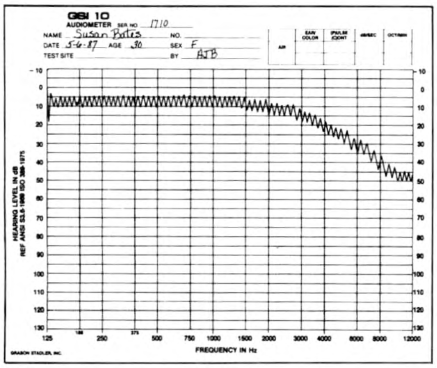

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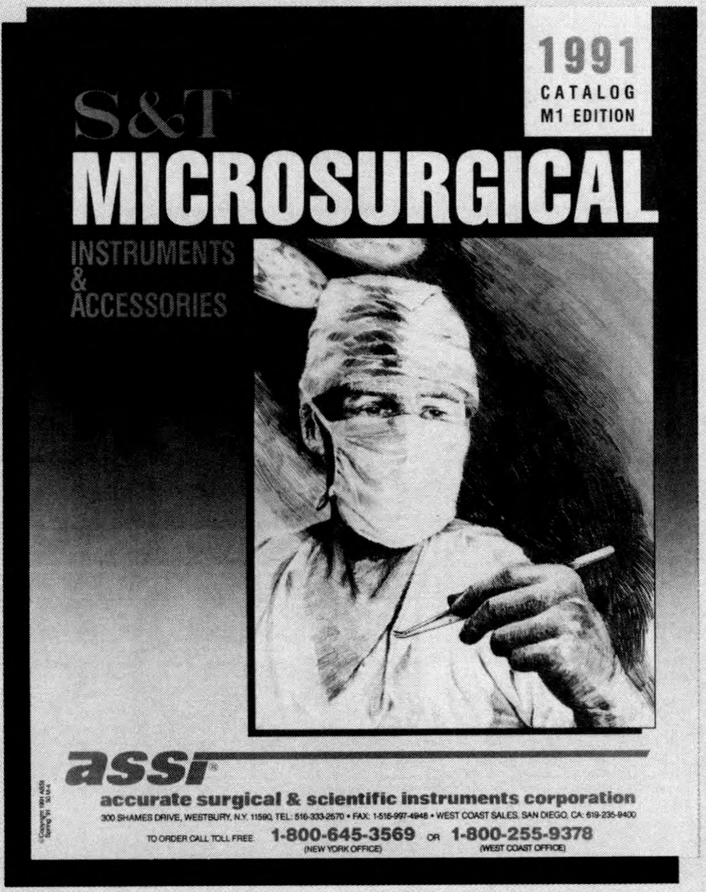
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PREDICTING RADIORESISTANCE IN EARLY GLOTTIC SQUAMOUS CELL CARCINOMA BY DNA CONTENT

MARGARET A. WALTER, MD
GLENN E. PETERS, MD
STEPHEN C. PEIPER, MD
BIRMINGHAM, ALABAMA

Nuclear DNA content has been implicated as a prognostic factor in an increasing number of tumor types. Current data on the role of DNA content in head and neck carcinoma are conflicting and incomplete. To evaluate the role of DNA content in predicting radioresistance, 29 patients with T1N0M0 squamous cell carcinoma of the glottic larynx who had undergone uniform curative radiotherapy and whose clinical outcome was known had flow cytometric analysis for DNA content performed on their tumors with paraffin-embedded archival tissues. Five aneuploid lesions and 24 diploid lesions were identified. All aneuploid lesions occurred in radioresistant tumors. The probability of an aneuploid tumor failing radiotherapy was highly significant at $p = .016$. No DNA discordance was found in a sampling of half of the radioresistant lesions' pretreatment and recurrent specimens, for a 100% predictive value of moderate statistical power. On the basis of these findings, patients with aneuploid T1 glottic lesions should be referred for primary surgical therapy.

KEY WORDS — aneuploidy, diploidy, DNA, flow cytometry, glottic carcinoma.

INTRODUCTION

Treatment strategies for squamous cell carcinomas of the upper respiratory tract are based on histopathologic classification and the extent of disease (stage). The prognosis for patients with localized disease, stage T1N0M0, is favorable, with cure rates of 90% to 94% achievable with either surgical procedures or radiotherapy.[1] In the instance of localized carcinomas of the true vocal cord, radiotherapy may be preferable because the functional performance spared is superior.[2] A small but significant group of patients have tumors with populations of radioresistant cells that lead to recurrence after radiotherapy. Currently, there is no means to identify this group of patients who require definitive surgical excision at the time of diagnosis.

It is evident that biologic aspects of tumor cell heterogeneity cannot be discerned from routine pathologic examination. Numerical genetic abnormalities, as determined from an abnormal DNA content, a feature unequivocally linked to malignancy, have been associated with adverse biologic and clinical features in a growing number of tumor types.[3]

We employed flow cytometry to analyze the DNA content of archival materials from known radiosensitive and radioresistant tumors to determine whether flow cytometric analysis furthered our classification and staging. Aneuploidy was highly predictive of relapse following radiotherapy in a group of patients with recurrent disease. However, it was not observed in a control group of patients who remained free of disease. Among patients with radioresistant tumors, those with aneuploid tumors tended to have a shorter disease-free interval than those with diploid tumors. This study confirms the use of flow cytometric analysis of DNA content in the evaluation of patients with carcinoma of the glottis.

SUBJECTS AND DESIGN

The records of patients with localized squamous cell carcinoma of the true vocal cord (American Joint Committee on Cancer stage T1N0M0) treated with curative radiotherapy were reviewed with approval by our Institutional Review Board. All patients received radiotherapy to the larynx via a 4-mV linear accelerator through opposed lateral ports at a dose of 1.8 to 2.0 Gy per day to a total of 64 to 70 Gy. Of this population, 14 patients with recurrent tumors were identified. A control group matched for stage, age, sex, and race was composed of 15 patients in whom an identical radiotherapy regimen was curative. The follow-up for the latter group ranged from 2 to 6.4 years (mean, 3.0 years). The specifics of the patient populations are presented in Table 1. Patients with inadequate follow-up, evidence of metastasis, a second primary tumor, or inadequate tumor mass for nucleii extraction were excluded from the study.

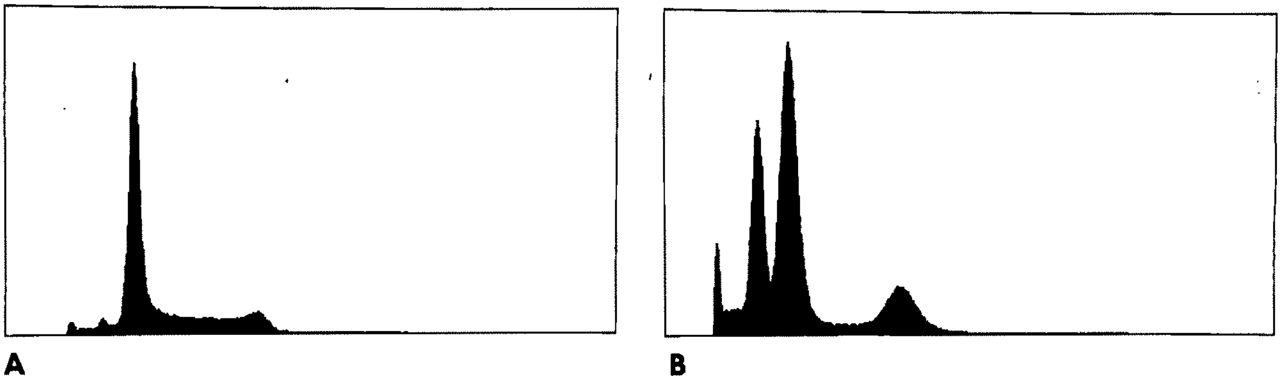
Within the group of patients with radioresistant

TABLE 1. PATIENT DATA

	Radioresistance	*Radiosensitivity*
No. of pts	14	15
Age (range)	57 y (41-82 y)	62 y (52-76 y)
Sex	12 M, 2 F	14 M, 1 F
Race	10 white, 4 black	12 white, 3 black
Vocal cord	7 R, 7 L	8 R, 7 L

No statistically significant difference was found between two groups in age, sex, race, or vocal cord site. Age is given at time of pretreatment diagnosis.

From the Department of Surgery, Division of Otolaryngology (Walter, Peters) and the Departments of Pathology and Medicine (Peiper), University of Alabama, Birmingham, Alabama.



Histograms of DNA content. A) Diploid. B) Aneuploid.

tumors, both pretreatment and recurrent lesions were adequate for analysis in seven. When possible, multiple samples were analyzed for each patient in parallel to ensure internal consistency and to maximize sampling the tumor. Reexamination of the histopathologic findings confirmed that all tumors were squamous cell carcinomas. There were no significant differences between the histologic features of the tumor in the radiosensitive and radioresistant groups. Final selection of tissues for extraction of nucleii was based on histologic review of hematoxylin and eosin–stained slides by the senior pathologist-author to determine adequacy of tumor mass and density within the paraffin-embedded tissues. Both preparation of specimens and analysis of results were done blinded to patient and group. Determination of DNA content, DNA index, and cell-cycle kinetics were performed on all tumors.

TECHNIQUE

Deparaffination and nucleii extraction for DNA analysis was accomplished with a modified method of Hedley et al[4] and two xylene exchanges of 5 mL each for 10 minutes at room temperature followed by progressive exchanges of 5 mL each of 100%, 95%, 70%, and 50% ethanol at room temperature for 10 minutes each. The specimens were then washed twice with distilled water and suspended in 1 mL of 0.5% pepsin in 0.9% sodium chloride adjusted to pH 1.5 with 2N hydrochloric acid in a 37°C bath for 1 hour. Samples were homogenized with a Pasteur pipette stained with 3 mL of propidium iodide with 1% trinitrotoluene by the method of Vindelov et al[5] and were incubated in the dye overnight. Samples were strained through a 30-μm fine-mesh filter and processed through the flow cytometer. Samples measuring at least 10,000 cells were considered for analyses.

Nuclear DNA content was measured with an EPICS C flow cytometer (Coulter Electronics, Inc, Hialeah, Fla) equipped with a 5-W argon laser run at a wavelength of 514 nm. Fluorescence was collected by a band pass filter at 488 nm. The instrument was standardized with standard microspheres and normal leukocytes.

Each block served as its own control: tumors were considered diploid if they had a single G0/G1 peak, since all specimens contained a mixture of tumor cells and normal tissues. The tumor was considered aneuploid if more than one G0/G1 peak could be discriminated. In aneuploid cases, the DNA index was calculated as the quotient of the peak channel of the aneuploid population over the peak channel of the diploid population. In the case of aneuploid tumors, the G0/G1 peak with the smaller coefficient of variation was considered to be the normal population since tumor populations are more heterogeneous.

RESULTS

Flow cytometric analysis of the tumors from the 29 patients studied revealed that 24 had a single G0/G1 peak, indicative of a diploid DNA content (see Figure, A). An additional, aneuploid population was identified in 5 patients. A representative histogram is shown in the Figure (B). When multiple specimens from each patient were analyzed, no examples of discordant DNA content were noted. The coefficient of variation, an indicator of specimen selection and laboratory technique, averaged 6.35 (range, 3.6 to 12.4), with many values as low as those obtained from fresh specimens.[6]

TABLE 2. RESULTS OF DNA TESTING OF RADIORESISTANT LESIONS

Pt No.	*Age*	*Race*	*Sex*	*DNA Status*	*Time to Recurrence (mo)*
1	73	W	M	Diploid	9
2	45	B	M	Suggested aneuploid	9
3	53	W	M	Aneuploid	6
4	82	W	M	Diploid	18
5	48	W	M	Aneuploid	4
6	67	W	M	Diploid	8
7	57	B	M	Aneuploid	6
8	71	W	M	Diploid	30
9	44	W	M	Aneuploid	7
10	49	W	M	Diploid	13
11	67	B	F	Diploid	32
12	41	W	F	Diploid	24
13*	52	W	M	Diploid	20
14	55	B	M	Diploid	8

*Finished radiotherapy over slightly prolonged time course of 71 days.

TABLE 3. RESULTS OF DNA TESTING OF RADIOSENSITIVE LESIONS

Pt No.	*Age*	*Race*	*Sex*	*DNA Status*	*Follow-up*
15	64	W	M	Diploid	2 y 9 mo
16	69	W	F	Diploid	2 y 10 mo
17	61	B	M	Diploid	3 y 5 mo
18	76	W	M	Diploid	3 y 2 mo
19	52	B	M	Diploid	4 y 2 mo
20	75	W	M	Diploid	3 y 1 mo
21	63	W	M	Diploid	6 y 4 mo
22	53	W	M	Diploid	4 y
23	64	W	M	Diploid	2 y 3 mo
24	59	W	M	Diploid	3 y 9 mo
25	55	W	M	Diploid	3 y 10 mo
26	57	W	M	Diploid	2 y
27	64	W	M	Diploid	3 y 1 mo
28	57	W	M	Diploid	2 y 8 mo
29	69	B	M	Diploid	2 y 10 mo

The radioresistant and the radiosensitive lesions were compared. All of the patients with aneuploid tumors were in the radioresistant group, while the radiosensitive group was composed exclusively of patients whose tumors were diploid (Tables 2 and 3). The DNA index of aneuploid tumors averaged 1.60 (range, 1.30 to 1.78).

The tumor from patient 2 showed an abnormal DNA histogram that had a significant population of cells with a DNA content greater than the G0/G1 peak, although an aneuploid component could not be discriminated with certainty. This patient's tumor was considered to be genetically abnormal and highly suggestive of aneuploidy.

The probability of an aneuploid lesion failing radiotherapy was found to be highly significant ($p = .016$) by Fisher's exact test. No significant difference in cell-cycle kinetics, S-phase fraction (24% versus 22%), or G2/M phase (13% versus 17%) could be discerned between the radioresistant and radiosensitive tumors.

Among patients with radioresistant tumors, those with aneuploidy were more likely to have a shorter disease-free interval ($p = .0054$). Patients with aneuploid lesions tended to be younger, but this fact was not statistically significant ($p = .07$) (Table 4). No difference in cell-cycle kinetics was seen between the diploid and aneuploid lesions in the radioresistant group as judged by the percent of cells in S-phase (23.7% versus 23.9%) or G2/M phases (14% versus 12%).

Within the radioresistant group, five patients with diploid tumors and two patients with aneuploid tumors had data available from both pretreatment and recurrent specimens. In every instance there was concordance of DNA content between the pretreatment and recurrent tumors; thus, the existing evidence would indicate that radiotherapy did not alter DNA content.

TABLE 4. STATISTICAL ANALYSIS OF RADIORESISTANT TUMORS

	Diploid	*Aneuploid*	*Fisher's Exact Test*
Number	9	5	
Disease-free interval	18.0 mo	6.4 mo	p = .0054
Age (average)	61.4 y	49.6 y	p = .07

DISCUSSION

Aneuploidy is a predictor of aggressive clinical behavior in many malignant tumors. The role of ploidy analysis in tumors of the head and neck is controversial. Our findings suggest that the presence of aneuploidy may provide critical insight into the biologic behavior of these tumors. All patients in our study had localized tumors of the true vocal cord and received a uniform regimen of curative radiotherapy. Previous studies of squamous cell carcinoma of the head and neck are flawed because conclusions are drawn from comparisons made between patient groups without appropriate control for site, treatment regimen, or stage of disease. Moreover, many series contain small numbers of patients.

Comparison to a previous study reported by Guo and DeSanto[7] of 296 surgically treated cancers from oral, pharyngeal, and laryngeal sites showed a survival advantage of diploic tumors at each stage. However, the data were not analyzed by anatomic site, and adjuvant radiotherapy, at widely varying dosages, was administered to some patients.

Goldsmith and Cresson[8] evaluated a series of 24 patients with glottic tumors that varied with respect to therapy and stage. Although a favorable prognosis was associated with tumors that had a high DNA content, the results must be interpreted with caution because the study was heavily weighted to patients with advanced-stage lesions and was not controlled for treatment regimen. In contrast to the present series, only 5 of the patients had stage I tumors; 3 of these received radiotherapy while 2 underwent hemilaryngectomy. Thus it is difficult to extend the results to apply to patients with early disease when there is an option of therapeutic modalities.

Holm[9] evaluated 45 patients with carcinomas of the head and neck with various anatomic sites, stages, and treatment regimens and found no correlation between response to radiotherapy and DNA content. This population contained 4 patients with laryngeal carcinoma. Although 2 had stage I tumors that were aneuploid and both patients were free of disease, 1 received primary radiotherapy and the other received combined surgical treatment and radiotherapy. The failure to observe a relationship between radioresistance and aneuploidy in this series, as well as in that of Guo and DeSanto,[7] may have resulted from the obscuring of an association present in early tumors of a specific site by the inclusion of all head and neck tumors regardless of stage.

The aggressive nature of aneuploid laryngeal carcinomas localized to the true vocal cord is supported by a high probability of radioresistance, a significantly shortened disease-free interval, and the tendency to occur in a younger age group.

Unlike previous reports, this study is well controlled for both specific anatomic site, stage, and treatment regimen, as well as patient population characteristics. Current treatment regimens for such early tumors yield excellent cure rates with either definitive radiotherapy or hemilaryngectomy. Since patients with aneuploid lesions have a high probability of failing radiotherapy, they should be referred for alternative primary surgical therapy.

By studying a tumor that is manifested by early symptoms such as hoarseness, diagnosis prior to the occurrence of extensive heterogeneity of the tumor population is probable. As evidenced by our finding of concordance in the tumor DNA stem line between pretreatment and recurrent tumors, these aggressive lesions were probably aneuploid from the initiation of malignant change. This discovery may distinguish them from advanced-stage aneuploid lesions, which may have become so through selection of a more aggressive tumor subpopulation over time.

CONCLUSION

T1N0M0 squamous cell carcinomas of the glottic larynx with aneuploid DNA content are more aggressive tumors than their diploid counterparts because radioresistant populations are invariably present. All of these aneuploid tumors were found to recur in spite of curative radiotherapy. The patients had a significantly shorter disease-free interval and tended to be younger.

There are many questions that remain to be answered in regard to the role of DNA content in glottic carcinoma. To demonstrate conclusively that radiotherapy does not alter DNA content, a larger number of patients would need to be evaluated at diagnosis and recurrence. Although we found a high probability of radioresistance among these aneuploid lesions, we cannot state unequivocally that aneuploidy is predictive of radiotherapy failure, because half of the recurrent group had only posttherapy data available. A larger prospective study of pretreatment lesions would need to be analyzed to strengthen predictive value.

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RECURRENT PAROTITIS AND SIALECTASIS IN CHILDHOOD

CLINICAL, RADIOLOGIC, IMMUNOLOGIC, BACTERIOLOGIC, AND HISTOLOGIC STUDY

SUNE ERICSON, DMD, PHD
BIRGITTA ZETTERLUND, MD
JAN ÖHMAN, MD
JÖNKÖPING, SWEDEN

Twenty children with juvenile recurrent parotitis, between 3 months and 16 years of age at onset, were followed up over a period of 7 to 22 years. Radiologic, histopathologic, cytologic, immunologic, and bacteriologic studies were performed to investigate the cause of sialectasis, commonly found in juvenile recurrent parotitis, and the pathogenesis of the disease. It was considered that a combination of a congenital malformation of portions of the salivary ducts and infections ascending from the mouth following dehydration of the children are contributory to the pathogenesis of the disease. The results of the investigations into the cause of the disease appear to exclude an autoimmunologic response or an allergic condition, an immature immune response, mumps, a sensitivity to upper respiratory tract infection, and familial factors.

KEY WORDS — bacteriology, children, cytology, histopathology, immunology, recurrent parotitis, sialectasis, sialography.

INTRODUCTION

Juvenile recurrent parotitis (JRP) is rare, but next to mumps it is the most common inflammatory salivary gland disease of childhood.[1,2] The condition is characterized by periodic acute or subacute swelling of the parotid gland, usually accompanied by pain as well as fever and malaise. The exacerbations are predominantly unilateral, and when bilateral, the symptoms usually are more prominent on one side. Between the attacks the child is free from subjective symptoms.[3-8]

The disease usually starts in a child between 5 and 7 years of age, but earlier or later occurrence has been observed.[2,4,6,7,9] Exacerbations may occur over many years and usually manifest themselves every 3 to 4 months — with great individual variations — when the child is within an active period of the disease.[8,9] After puberty the symptoms usually subside and the disease may resolve completely.[2,4,7-9] However, there are also persistent cases.[8-12]

The morphologic condition of the affected glands in JRP reveals areas with massive infiltration of lymphocytes with lymph follicle formation.[1,4,7,13] There are cystically dilated intraglandular ducts, which in the sialographic image correspond to small spherical collections of contrast medium, called sialectases.[4,7,13,14] Whether these changes are the cause or the result of the recurrent exacerbations of the parotitis is still under discussion. Among factors that have been considered are congenital malformation of the parotid ducts,[6,7,13-17] heredity,[6,7,11,18,19] primary or secondary infection,[1-8,20-23] allergy,[19,24,25] and local manifestation of systemic immunologic diseases.[2,7,26]

In this report we have prospectively studied the course of the disease and analyzed some microbiologic, morphologic, and immunologic factors in order to elucidate the pathogenesis of the JRP and subsequent therapeutic approaches.

PATIENTS AND METHODS

Patients. The test group comprised 20 children: 8 girls and 12 boys between 3 months and 16 years of age (mean, 7.2 years) when first seen and examined in the Ear, Nose and Throat Department (ENT unit). The ages at the first attack of the disease, at

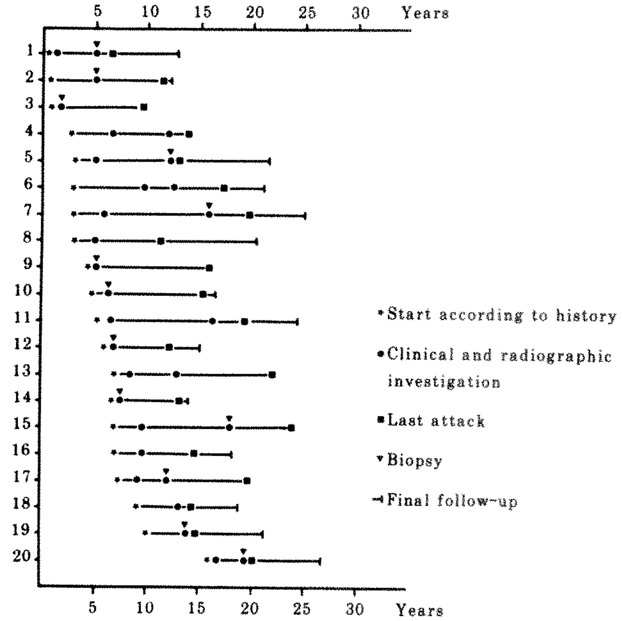

Fig 1. Schematic drawing illustrating age at first attack, at sialography, at biopsy, and at end of follow-up.

From the Department of Dental and Maxillofacial Radiology, Institute for Postgraduate Dental Examination (Ericson), and the Departments of Pathology (Zetterlund) and Otorhinolaryngology (Öhman), County Hospital, Jönköping, Sweden.

REPRINTS — Sune Ericson, DMD, PhD, Box 1030, S-551 11 Jönköping, Sweden.

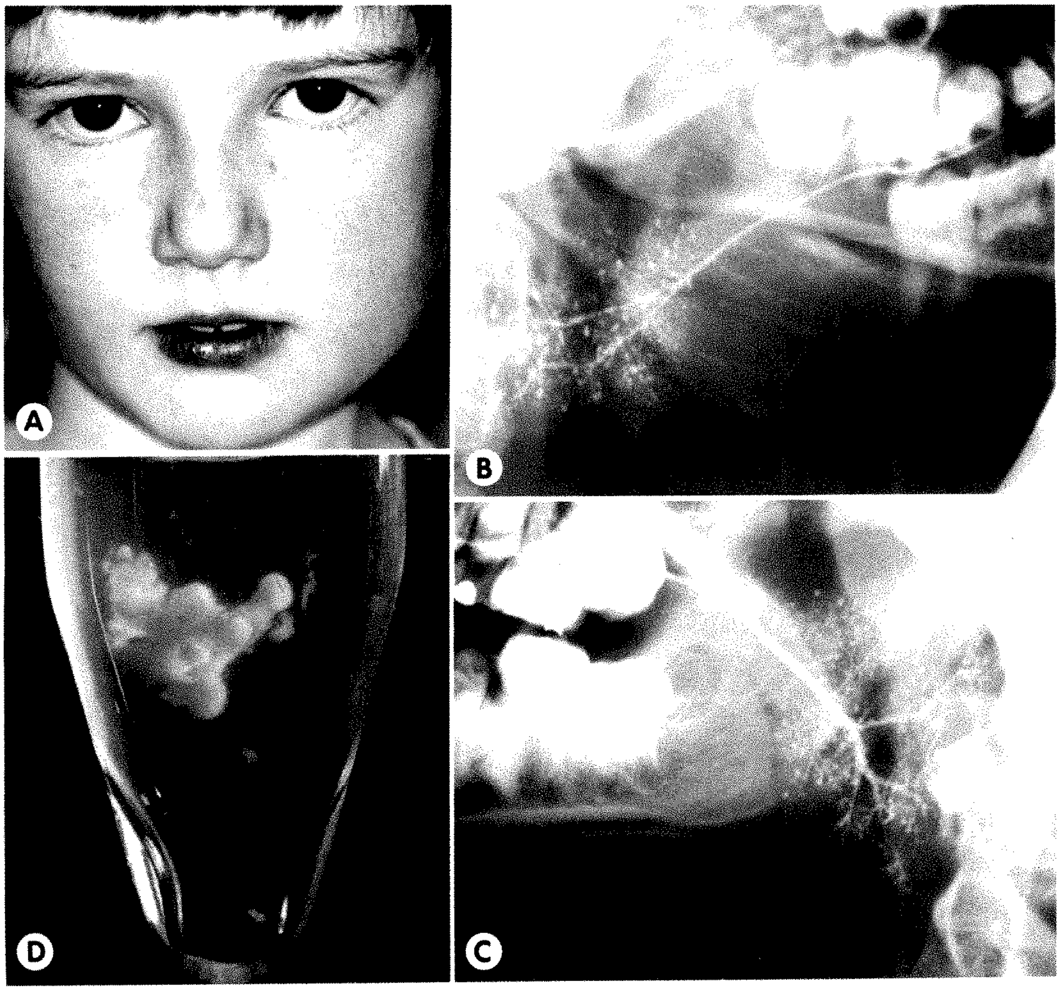

Fig 2. (Patient 6) Girl, 10 years of age, with unilateral symptoms of juvenile recurrent parotitis on left side. A) Swelling of left parotid gland. B,C) Sialograms of B) left and C) right parotid glands, with multiple sialectases in parenchyma. Main duct has normal appearance. D) Sample of parotid saliva from left gland in symptom-free phase showing small flakes and balls of organic material.

clinical and radiographic investigations, at biopsy, and at final attack, as well as the length of follow-up, are given in Fig 1. At the end of the follow-up the age of the subjects ranged from 9 to 25 years.

The case histories of the patients were obtained from the parents at the first visit. In some cases the symptoms of the disease had been mistaken for mumps and thus had existed for some time before the first visit to our clinic. The last follow-up data were obtained by telephone interviews.

Apart from the test group, parents, brothers, and sisters in three families — in all, 11 individuals — were investigated clinically by sialography and some laboratory tests. These subjects acted as controls. The familial aspect of possible salivary gland disease was further addressed by interviews with the parents of the 20 children in the test group.

Clinical Investigations. The children in the test group were clinically examined at least three times, one of which was during an acute phase (Fig 2A). The other examinations were made in a nonacute phase when subjective signs or symptoms of the disease were not apparent (Fig 2C,D).

Radiographic Investigations. Sialographic examinations of both parotid glands were performed in all children. Sialography was performed soon after the first consultation in the ENT unit when the patients were in a quiescent phase of the disease. During follow-up 10 patients had further sialography (Fig 1).

The parotid glands were recorded in lateral and frontal projections (Figs 2B,C and 3). Water-soluble contrast medium was used, and exposures were made during the filling and emptying phases (Fig 4A,B). The condition of the ductal system was assessed, and the presence and size of sialectases in the parenchyma were recorded.

Laboratory Investigations. Hemoglobin concentration, erythrocyte sedimentation rate, red and white total and differential cell counts, levels of total protein and serum electrophoresis, antinuclear antibody studies, and tests for rheumatoid factor

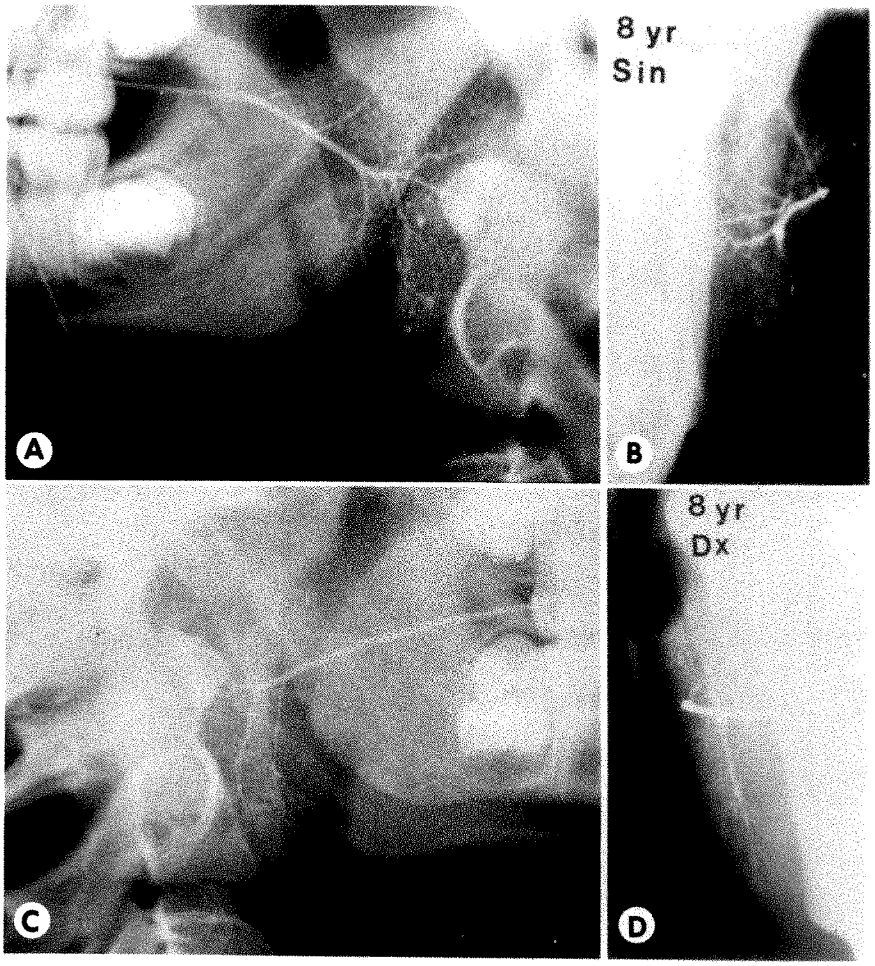

Fig 3. (Patient 9) Boy, 8 years of age, with unilateral symptoms of juvenile recurrent parotitis on left side. A,B) Sialograms of left (Sin) parotid gland in A) lateral and B) anteroposterior projection showing multiple punctate sialectases. Main duct has normal appearance. C,D) Sialograms of right (Dx), symptomless parotid gland. Normal appearance.

(RF), as well as Wassermann's reactions, were done according to the routine procedures of the hospital.

Determination of Antibodies. Serum from the patients was analyzed for the following autoimmune antibodies: antinuclear (ANA), smooth muscle (SMA), parietal cell (PCA), and salivary gland (SGA). The indirect immunofluorescence standard technique with rabbit FITC-labeled antihuman immunoglobulin (Ig) M and IgG antibodies was used to detect antibodies of IgM and IgG classes. Furthermore, the IgM and anti-dsDNA antibody (anti-dsDNA) were investigated. Unfixed cryostat sections from a nondiseased parotid gland as well as from a patient gland were used for determination of SGA. The initial serum dilutions were for ANA, 1:10; AMA, SMA, and PCA, 1:25; RF, 1:16; and anti-dsDNA, 1:10. Serum antibodies against mumps, virus, and Epstein-Barr virus (anti-EBV) were determined by complement fixation tests. Anti-streptolysin O (ASO) and antistaphylococcal alpha toxin were determined by routine procedures.

Bacteriologic Investigation. Microbiologic investigations of saliva were done in all patients and in four healthy controls. The children had not had antibiotics in 4 weeks before the culturing.

The proximal part of the parotid main duct was cannulated. A sterile plastic tube was inserted in the duct 2 to 3 cm and the secretion of saliva was stimulated gustatorily by citric acid.[27,28] Two samples of saliva were collected after a stimulation period of 4 to 5 minutes, put into a transportation medium, and cultured aerobically and anaerobically within 4 hours.

Biopsy and Histologic Examination. Wedge biopsies were obtained from the posterior aspect of 20 parotid glands from 13 children with JRP. These were done with the aim of correlating the histopathologic findings with the radiographic findings, and they enabled immunohistochemical tests to be performed. The specimens, 2 to 7 mm in diameter, went through the routine procedure for paraffin embedding. Six to eight consecutive levels were cut from each specimen and were stained according to our van Gieson method routine.

Polyclonal antibodies against secretory IgA, salivary amylase (Nordic Immunological Laboratories, Holland) and IgA, IgG, and IgM (Dakopatts, Denmark) were applied to most of the specimens, and the reaction was made visible with the indirect peroxidase method and ethyl carbazole as the color substrate. Monoclonal antibodies against B lymphocytes and T lymphocytes in paraffin sections

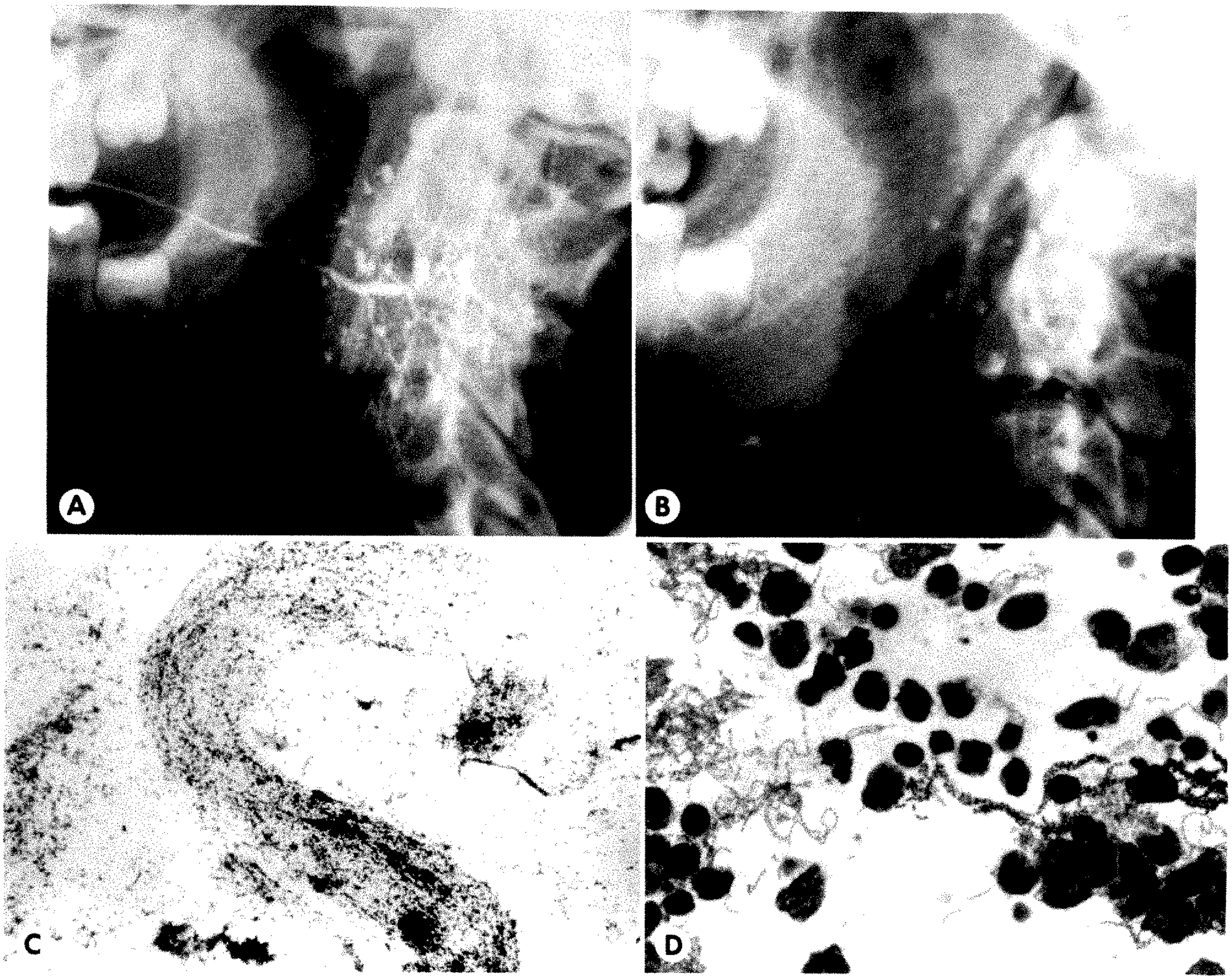

Fig 4. (Patient 17) Girl, 13 years of age, with unilateral symptoms of juvenile recurrent parotitis. A) Sialogram of left parotid gland with multiple globular sialectases. Main duct normal. B) Retention of water soluble contrast medium 5 minutes postinjection. C) Smear of saliva from left parotid gland with unilateral juvenile recurrent parotitis collected in symptomless phase showing cluster of cells and mucus (original x25). D) High-power view of lymphocytes and chains of bacteria in smear (original x250).

(UCHL1, L 26 and CD 45R, Dakopatts) were used in a few cases. The ABC method (Vector Laboratories, Burlingame, Calif) was used to visualize the reaction.

Exfoliative Cytology of Saliva. Saliva collected by cannulation from one or both parotid glands (minimum amount, 1 mL) in 16 of the children was centrifuged, and a smear was applied to glass and fixed by 95% ethyl alcohol for 30 minutes or dried in air. The specimens were stained for cytologic examination according to the methods of Papanicolaou and May-Grünwald-Giemsa, respectively.

RESULTS

Clinical Findings. Figure 1 and Table 1 list the clinical and anamnestic data of the 20 patients. Their ages at onset of the parotid swelling ranged from 3 months to 16 years. The number of attacks varied individually. The frequency rate remained fairly constant up to puberty, with peaks during the first years at school. For all children with the exception of 2 (patients 1 and 3), the swelling was associated with severe pain, fever, and malaise at the first consultation. Penicillin V was prescribed for all 20 children when attacks recurred. Simultaneous bilateral glandular swelling, less prominent on one side, was apparent in 8 children at the initial consultation in the ENT unit (Table 1). During the follow-up period patient 3 presented with a bilateral swelling.

At the last follow-up 5 children (patients 2, 3, 4, 9, and 14) reported no substantial change, and 15 (75%), an improvement. Eleven (55%) of the latter did not experience any attack in 2 years prior to the last follow-up study (Fig 1). Two individuals with severe sialographic changes had had exacerbations after the age of 20.

The case histories revealed that two children suffered from 1) allergy and 2) asthma and hypersensitivity to furs, respectively (patients 6 and 9). Four suffered from more than five upper respiratory tract infections (URTIs) per year (patients 5, 6, 16, and 18). Some of the parents had observed that URTIs

TABLE 1. DISEASE HISTORY AND SIALOGRAPHIC FINDINGS IN CHILDREN WITH JUVENILE RECURRENT PAROTITIS AT PRIMARY INVESTIGATION

Pt No.	Sex	Most Attacks Per Year	Most Affected Gland		Less Affected Gland	
			Symptoms	Sialectasis	Symptoms	Sialectasis
1	M	2-3	+ +	+ +	–	+
2	M	8-10	+ + +	+ + +	–	–
3	F	3-4	+ +	+ + +	–*	(+)
4	F	6-7	+ + +	+ +	–	+ +
5	F	2-3	+ + +	+ + +	+ +	+ +
6	F	2-3	+ + +	+ + +	–	+ +
7	M	9-10	+ + +	+ + +	+ + +	+ +
8	M	6-7	+ + +	+ +	–	+
9	M	3-4	+ + +	+ + +	–	–
10	M	2-3	+ + +	+ + +	+ + +	+ + +
11	M	2-3	+ + +	+ +	+ + +	+ + +
12	F	8-10	+ + +	+ + +	+ +	+ +
13	M	5-6	+ + +	+ +	+ +	+ +
14	M	3-4	+ + +	+ +	+ +	+ +
15	M	2-3	+ + +	+ +	+ + +	+ + +
16	F	2-3	+ + +	+ + +	–	+ +
17	F	3-4	+ + +	+ + +	–	–
18	F	3-4	+ + +	+ + +	–	+ +
19	M	4-5	+ + +	+ + +	–	+
20	M	3-4	+ + +	+ + +	–	+ +

Symptoms: – indicates no symptoms, + indicates few attacks of swelling, without pain and fever, + + indicates many attacks of swelling with or without pain and fever, + + + indicates many attacks of swelling, pain, fever, and malaise, with antibiotics administered. Sialectasis: – indicates no findings, + indicates few punctate sialectases (< 2 mm), + + indicates many punctate sialectases (< 2 mm), + + + indicates multiple punctate and globular sialectases (> 2 mm).

*Symptoms during follow-up.

preceded the swelling, others that the swelling occurred without relation to URTIs. Earlier infection with mumps was reported in 14 of the cases.

By history there was no evidence of a familial salivary gland disease. Thus, none of the parents, brothers, and sisters had had salivary gland involvement apart from mumps.

Sialographic Findings. The results of the radiographic investigations at sialography are listed in Table 1 and illustrated in Figs 2B,C; 3; 4A,B; and 5.

The primary radiographic examination showed multiple sialectases on the most affected side in all children. The sialectases were uniform in size, mostly measuring 1 to 2 mm in diameter, and in 4 cases up to 5 mm and scattered throughout the gland. In 5 of the 20 most affected glands the main duct was slightly to moderately dilated. In glands in which sialectasis was seen, the peripheral intraglandular ducts were partly invisible. Cavitary sialectases and destructive changes were not seen.

Sialography of both parotid glands was performed irrespective of the persisting clinical signs or symptoms and medical history (Table 1). Of the 12 children without symptoms from the opposite gland the sialographic investigation revealed sialectases in 8 cases (Fig 2A-C) and normal images in 4 (Fig 3C,D). The sialectases were on average fewer and smaller in size in the glands free of clinical symptoms.

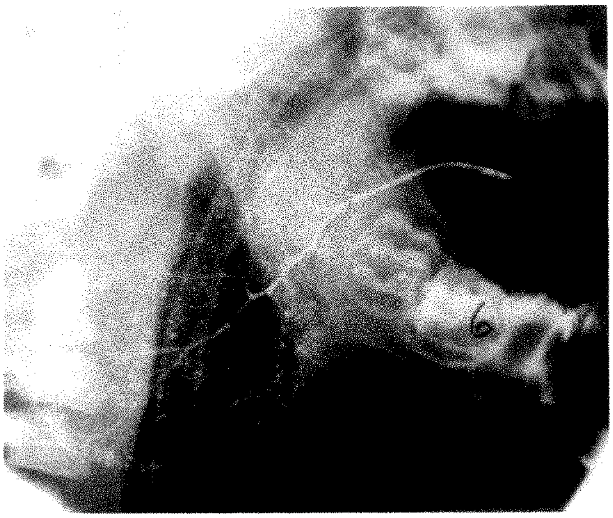

Fig 5. (Patient 1) Boy, 6 months of age (6), with bilateral symptoms of juvenile recurrent parotitis. Sialogram of right parotid gland shows enlarged gland with multiple sialectases.

Eight children had symptoms of JRP in both parotid glands. However, the changes were, with one exception, less prominent in the gland with least clinical involvement. Bilateral sialectases were found in one boy (patient 1) of 6 months of age (Fig 5).

The sialographic investigations of the parotid glands in 11 family members showed normal conditions.

Laboratory Findings. Results of routine laboratory tests were mostly normal. A few patients exhibited a slight rise in erythrocyte sedimentation rate. In the two allergic patients eosinophilia of 5% or above was noted. A slight increase in IgG and IgM was observed in three patients.

Findings of Antibodies. As expected in this young group of patients, no ANA, SMA, PCA, anti-dsDNA, or RF was detected. Neither was SGA demonstrated. Antimumps virus and anti-EBV were found in a pattern not differing from that of a healthy group corresponding in age. Neither ASO nor antistaphylococcal alpha toxin was found.

Salivary Bacteriologic Findings. All samples of saliva were collected during a nonacute (symptom-free) phase of the disease. There were 21 samples from glands with sialectases and earlier clinical symptoms of JRP, 4 samples from glands with sialectases without known symptoms, and 3 from glands without symptoms or signs of JRP. The results of the saliva cultivation from the 28 glands are listed in Table 2.

White flakes or balls of soft material (Fig 2D)

TABLE 2. CORRELATION OF BACTERIOLOGIC AND SIALOGRAPHIC FINDINGS IN CULTURED SALIVA FROM 20 CHILDREN WITH JUVENILE RECURRENT PAROTITIS IN NONACTIVE PHASE OF DISEASE

	Saliva Ocular Inspection			*Saliva Cultures*		
Sialographic Image	*No.*	*Clear*	*Small Flakes*	*No.*	*Negative*	*Positive*
No symptoms or sialectasis	4	4	0	3	3	0
Sialectasis without known clinical symptoms	8	7	1	4	2	2
Sialectasis with earlier clinical symptoms	28	6	22	21	4	17
Total	40	17	23	28	9	19

were seen in 23 of the 36 samples (64%) from glands with radiographic sialectases. Of these 23 samples 22 came from children with earlier attacks of JRP (Table 2). In cases with normal sialographs, the saliva was clear and no bacteria were found. Pus was not observed. Cytologic findings in the smear of saliva are reported below.

Bacteria were found in saliva from 17 of 21 glands (80%) with true JRP and in 2 of 4 samples from glands with sialectases without observed signs or symptoms of JRP (Table 2). Only two children with JRP (10%) and 6 of 25 (24%) of the glands with sialectases in which the saliva was analyzed microbacteriologically did not show growth (Table 2). The bacteria isolated are listed in Table 3.

Exfoliative Cytologic Findings of Saliva. Microscopic findings on salivary smears were mostly in accordance with radiographic appearance. When there was a finding of dilated ducts, the saliva from the corresponding gland contained large amounts of granulocytes. There were also some lymphocytes, and in about half the specimens (63%) bacteria were seen (Fig 4C,D). Cylindric epithelial cells were seen in a few specimens.

In five cases the cytologic results were not in accordance with the radiographic findings. In six smears from four children there was an acellular fluid on the slides, although the saliva was collected from glands with sialectasis. Four of these smears were from glands with sialectasis without clinical symptoms. Salivary smears from six healthy individuals not included in the study did not contain any cells.

Histologic Findings. The histologic changes were similar in all specimens. There were more or less dilated interlobular ducts with lymphocytic infiltration in the surrounding tissues (Fig 6). In most specimens there were lymph follicles in the infiltrates. The epithelium was mostly hyperplastic and pseudostratified cylindric, and in one case had mucous metaplasia. Lymphocytes from the surrounding tissue were invading the epithelium.

In all specimens there were also small collections of plasmacytes and lymphocytes inside the lobules, mostly near the intralobular ducts. Only in one specimen was granulocytic infiltration found.

The findings were in accordance with the radiographic picture of sialectases in 16 glands. The results of two biopsies showed no or insignificant duct dilatation although x-ray films had shown sialectases. As the biopsy was taken without correlation to sialographic finding, this outcome is not surprising. In these two cases (patients 2 and 12) there was severe inflammation, and in one case, there were also epithelioid cell granulomas (patient 12). Findings of a third biopsy (patient 15) in which x-ray films had shown sialectases revealed neither duct dilatation nor inflammation. In a fourth biopsy (patient 3) a severe inflammation and a duct dilatation were found, but an x-ray examination did not show obvious sialectasis. Patient 3 was a very young child (6 months of age) who later developed JRP.

In most of the specimens immunohistochemical staining was done for secretory IgA and salivary amylase. In our hands these investigations showed a weak staining of epithelium in the intralobular ducts with antibody against secretory IgA and a positive reaction in the serous glands for antibody against salivary amylase. There was no difference from the reactions in normal control parotid tissue from patients operated on for parotid cysts.

With antibodies to IgA, IgG, and IgM, we could identify some plasmacytes containing IgA in the periphery of the lymphoid infiltrates around the interlobular ducts and in small inflammatory cell col-

TABLE 3. BACTERIA ISOLATED FROM SELECTIVELY COLLECTED SALIVA FROM 19 GLANDS WITH SIALECTASIS IN 18 CHILDREN WITH JUVENILE RECURRENT PAROTITIS

Isolates	*No.*
Aerobic and facultative	
Cocci	17
α-Streptococci	2
β-Streptococci	1
γ-Streptococci	1
Pneumococci	4
Staphylococcus epidermidis	1
Bacilli	
Hemophilus influenzae	2
Hemophilus parainfluenzae	1
Anaerobic	
Veillonella	2
Cocci	8

No culture was performed in two children.

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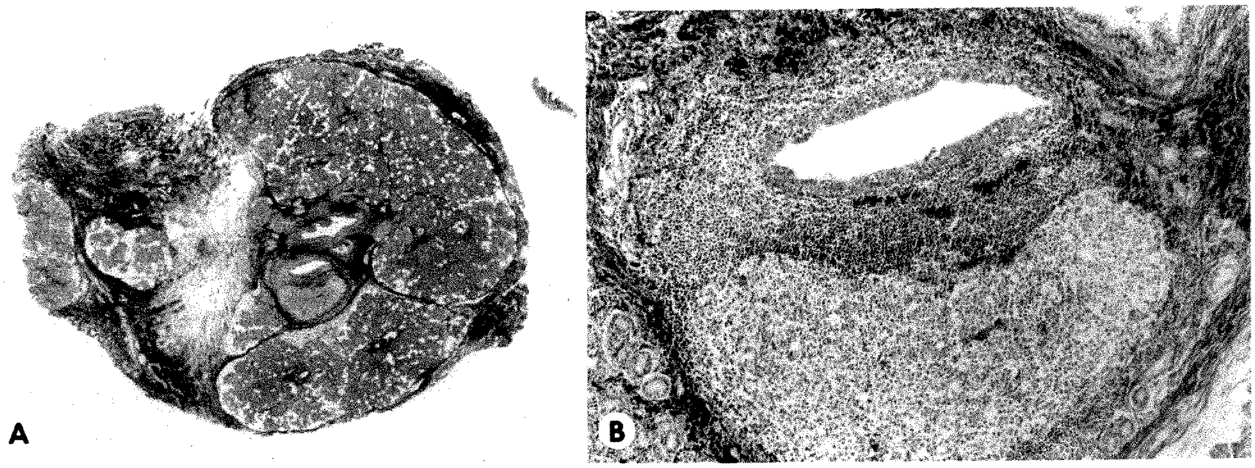

Fig 6. (Patient 3) A) Left ectatic ducts surrounded by lymphoid infiltrate with secondary follicles (original x25). B) High-power view of lymphoid nodule (original x250). Lymphocytes are also located inside epithelium.

lections inside the lobules. There were a few cells containing IgM but very few cells positive for antibodies against IgG.

Monoclonal antibodies reactive for B lymphocytes and T lymphocytes in paraffin sections were applied to sections from a few cases. It was confirmed that the lymphocytes were of the B type both outside the duct walls and in the epithelium. T lymphocytes were seen at the periphery of the lymphoid infiltration.

DISCUSSION

Juvenile recurrent parotitis is a rare disease fairly often interpreted as mumps in young children. In contrast to mumps the swelling recurs and usually affects the parotid gland unilaterally, and when bilateral, one gland is often affected less than the other. As shown by us and reported earlier,[2,6-9] the disease starts early in life, with a peak during the first years at school. From the follow-up it is also seen that exacerbations occur over the years, but at puberty there is a decrease in frequency in most cases, indicating a self-limiting character of the disease. These findings are in agreement with those of other investigators, which have shown that the disease clinically may disappear completely in adult life.[8,9,11] However, the sialographic changes remain mainly unaltered.[9]

It has been suggested that JRP may be of autoimmunologic origin.[2,7,26] The self-limiting nature of the JRP and the absence of SGA as well as the other investigated autoantibodies by serologic and immunohistochemical tests indicate that autoimmunity is a less probable cause in JRP. The results correspond in this respect with the findings of Kono and Ito[7] and with some other investigations.[10,12]

This study lends no support to the suggestion that JRP is an allergic condition or is a consequence of immature immune response, of mumps, or of sensitivity to URTIs.[7,8,23] However, viral URTI might yet be of significance to the pathogenesis by initiation of the disease through dehydration of the child, with reduced salivary secretion providing a ground for bacterial infection. At rest the parotid secretion is normally very low and much lower than the submandibular output[29,30]; this factor may explain the predominance of the parotid gland involvement.

The sialographic image was quite characteristic (Figs 2B,C; 3A,B; 4A,B; and 5), and in accordance with earlier reports the changes mostly appeared in the peripheral parts of the ductal tree.[3,7,9,10,14,31] Histologically, those parts correspond to the intralobular ducts.

There was a high relationship between clinical symptoms and multiple sialectases. In glands most affected by clinical exacerbations the sialographic changes also were more pronounced. In the opposite, clinically uninvolved glands, sialectases were found in 8 of 12 children. In the remaining 4 patients with symptoms only in one gland, no sialectasis was noted. Histologically, sialectases were found in one of the latter cases (patient 3). When found in glands clinically free of symptoms, the sialectases were smaller and fewer in number on the average. These observations support the contribution of a congenital factor in the cause of the disease as proposed by Bailey in 1945.[16]

The lymphoid infiltration has the characteristic appearance of mucosa-associated lymphoid tissue with invasion of epithelium and expression of B phenotype.[32] The histologic findings show a chronic inflammatory process in relation to localized duct dilatation. The findings give no support to the suggestion that the sialectases seen in the sialographs were due to ductal rupture and extravasation of injected fluid as proposed by others.[33] There were no signs of present or healed tissue destruction, and the ectases were always lined with intact epithelium. It therefore seems logical to assume that the spherical duct ectases preceded the inflammation. This is especially likely as the patients are children as young as 6 months of age and the clinical involvement is unilateral. However, manifest sialectases without chronic inflammation have not been found in our small biopsy specimens.

The fact that the lesion affects small children, even infants, also speaks for a congenital contributory factor in JRP, and sialectasis or its preliminary stages may be one among other factors in the pathogenesis of JRP, eg, predisposition for bacterial colonization.

Bacteria commonly found in the oral flora were cultivated frequently (80%) in saliva from glands with JRP in a nonactive phase of the disease, but also in two of four glands with sialectasis free from clinical symptoms. The histologic analyses of the salivary smears showed confirmatory results in relation to the true JRP glands. These findings show that most children with sialectasis, once infected, have a bacterial infection in their parotid ducts between attacks, and the species of bacteria indicate an ascending nature to the infection. Normally, bacteria are not found in saliva from healthy glands.

In four cases (patients 7, 14, 16, and 17) saliva from glands in the active phase of JRP was also cultivated. These samples showed a predominance of aerobic and anaerobic cocci in agreement with the findings from the symptom-free phase of the disease. No staphylococci were found. In retrospect it would have been of value to take culture specimens during acute episodes in all patients. The assumption that commensal bacteria were the cause of the infections might then have been further tested.

Balls of soft material were usually seen in saliva from glands with sialectasis. These aggregates of cells and mucus may form plugs and cause stagnation of the salivary flow and aggravate the inflammation and the parenchymal changes.

Familial and racial factors are said to play a role in JRP.[7,8,18,19] Our study does not give support for this assumption.

Regrettably, no preventive therapy against this disease is available. At the recurrences it is important to treat the acute inflammation of the gland to prevent further damage of the glandular parenchyma. In most cases penicillin V is effective. Theoretically, it can be questioned whether the administered antimicrobial therapy may have been inadequate, thereby promoting the formation of sialectasis. It should, however, be emphasized that the children included in this study responded promptly on all occasions to oral medication with penicillin V. Clinically, there was no obvious need to change the antibiotic. Staphylococcal bacteria generally do not form a major part of the oral flora of otherwise healthy children. The infections furthermore never had the character of a pronounced purulent parotitis, as seen in debilitated patients in whom a staphylococcal infection should be suspected. In these situations agents active against the staphylococcus, such as cloxacillin and flucloxacillin, should be the first choice.

It is also important to have close contact with the patients and their families because a regimen of massage, warmth, and use of chewing gum might be helpful. From the interviews it appeared that many of the grown children in this study reduced the attacks of JRP with massage of the parotid gland.

CONCLUSION

The results strongly indicate that sialectases found in cases of JRP precede the infection and constitute a site of little resistance. Congenital ectasia of portions of salivary ducts and infection ascending from the mouth are reasonable explanations of the parenchymal changes and the pathogenesis of JRP.

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Ann Otol Rhinol Laryngol 100:1991

ENDOSCOPIC SURGERY OF THE VIDIAN NERVE

PRELIMINARY REPORT

MOHAMED A. EL SHAZLY, MD
CAIRO, EGYPT

The anatomy, surgical technique, and difficulties of endoscopic vidian neurectomy are described. The procedure was carried out on 12 patients: 8 had resistant secretomotor rhinopathy and 4 had recurrent nasal polyposis. This technique is a minor surgical procedure with symptomatic relief and minimal postoperative morbidity.

KEY WORDS — endoscopic nasal surgery, endoscopic vidian neurectomy, vidian neurectomy.

INTRODUCTION

The value of vidian neurectomy in relieving the symptoms of vasomotor rhinitis is well established. This type of surgery has evolved over the last 30 years. There are a variety of approaches described, namely the classic transantral,[1] the transpalatal,[2] the transantral subperiosteal,[3] the blind transnasal,[4] and the microscopic transnasal.[5,6] The number of procedures suggests that none of these approaches is entirely satisfactory.

To avoid the drawbacks of the previous techniques, we used endoscopic nasal surgery to section the vidian nerve through the sphenopalatine foramen. This article will discuss the anatomy, the surgical technique and the difficulties of endoscopic vidian neurectomy. This procedure was done bilaterally on 12 patients with vasomotor rhinitis. Eight had resistant secretomotor rhinopathy and 4 had recurrent nasal polyposis.

RELEVANT ANATOMY

The vidian nerve carries parasympathetic fibers from the greater superficial petrosal nerve, and sympathetic fibers from the deep petrosal nerve around the internal carotid artery. It passes in the ptergygoid canal with the vidian artery. The canal is 1 cm long and has a funnel-like mouth at the posterior aspect of the pterygopalatine fossa. This opening and the foramen rotundum, situated 8 to 9 mm upward and laterally, are the only two foramina present at the posterior wall of the pterygopalatine fossa. They are separated from each other by a distinct vertical bony ridge forming the lateral aspect of the mouth of the pterygoid canal[7] (Fig 1).

TECHNIQUE

The procedure of transnasal vidian neurectomy is performed with a Karl Storz 30° rigid telescope, a sickle knife, a pair of curved scissors, a small periosteal elevator, a large curved sucker dissector, a right angled hook, a curette, and an isolated suction tip.

The procedure is done under general anesthesia using a hypotensive technique. The patient is lying in the reverse Trendelenburg position. The head is tilted toward the right side, facing the surgeon.

In those cases with extensive nasal polyposis, polypectomy is done, followed by intranasal ethmoidectomy. The nose is then prepared by packing with gauze soaked in epinephrine 1/200,000 to ensure good vasoconstriction.

By means of the telescope, the posterior end of the middle turbinate and the superior and middle meati are infiltrated with epinephrine of the same concentration. The sphenopalatine foramen, which is oriented at an angle of 15° to 20° with the sagittal plane,[5] is located 1) just behind or slightly above the attachment of the posterior end of the middle turbinate,[8] and 2) at the junction of the superior and lateral walls of the nasal cavity 12 mm above and also lateral to the superior border of the choana.[5]

Also, the superior turbinate acts as a pointer to the sphenopalatine foramen, located behind and above the middle turbinate (Fig 2). A valid landmark, observed by the author, is the constant convergence of some of the vessels of the lateral nasal wall toward the foramen. This is due to disappearance of the vessels into the sphenopalatine foramen. This is what could be called the vanishing point.

The foramen is carefully palpated and located with a blunted probe that pushes the intact mucosa before it. An incision is made with a sickle knife posterior to the expected posterior lip of the sphenopalatine foramen, as the mucosa at this site is relatively avascular.

Forward dissection of the mucoperiosteum is carried out by the large sucker dissector until the foramen is reached. The smaller dissector is used to free the soft tissues from the lips of the foramen. Little danger exists from dissecting near the sphenopalatine artery. This artery, the only notable vascular

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From the Department of Otolaryngology, Cairo University, Cairo, Egypt.

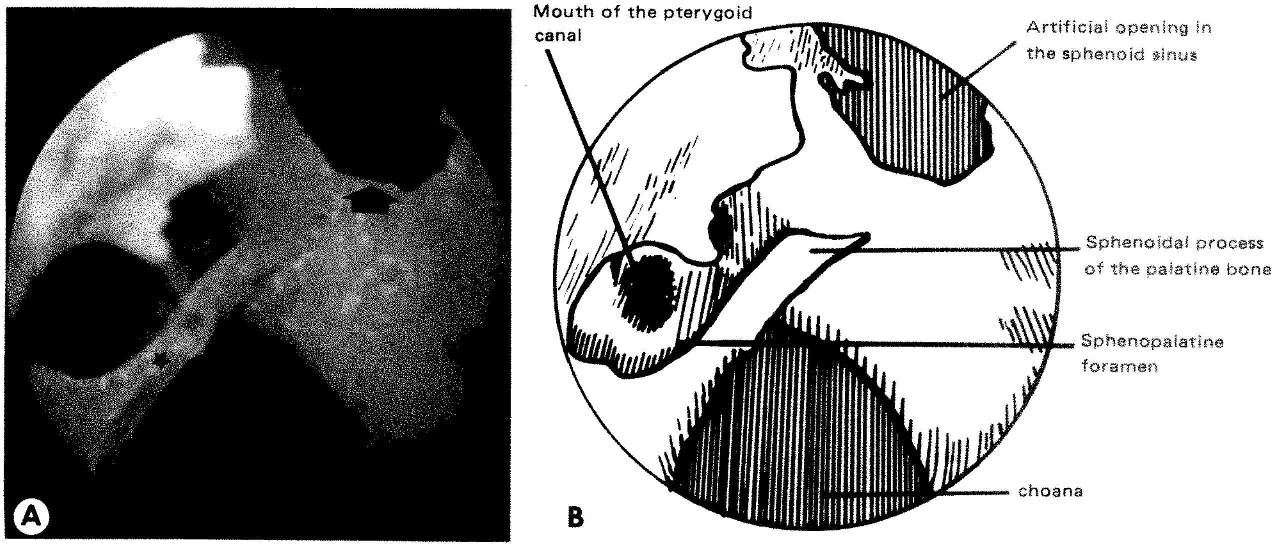

A
B
Mouth of the pterygoid canal
Artificial opening in the sphenoid sinus
Sphenoidal process of the palatine bone
Sphenopalatine foramen
choana

Fig 1. Mouth of pterygoid canal (small arrow on A) as seen by angled telescope 30° through sphenopalatine foramen. Shows posterior lip of sphenopalatine foramen (star on A) and artificial opening in sphenoid sinus (large arrow on A).

risk, is clothed in a lamina that protects it while the sphenopalatine foramen is being crossed.[5]

Dipping the dissector within the sphenopalatine foramen and advancing it in the posterior direction allows the separation of the periosteum of the pterygopalatine fossa from the lateral wall of the sphenoid process of the palatine bone. The mouth of the pterygoid canal is reached at the posterior wall of the pterygopalatine fossa and is located 5 to 6 mm posterior and lateral to the sphenopalatine foramen.[5] In case the sphenopalatine foramen is small, both the posterior and inferior lips (which are thinner than the anterior lip) are curetted to allow better exposure of the mouth of the pterygoid canal.

Next, the structures within the pterygopalatine fossa are pushed forward, stretching the vidian nerve out of its canal.

The nerve is isolated with the hook and cut with the curved scissors. Coagulation of the proximal stump is then carried out by using the isolated suction tip for 3 to 5 seconds (Fig 3).

At the end of the procedure, the mucoperiosteum of the lateral nasal wall is then repositioned and covered with Gelfoam. This Gelfoam is retained in place by a small pack that is removed after 6 hours.

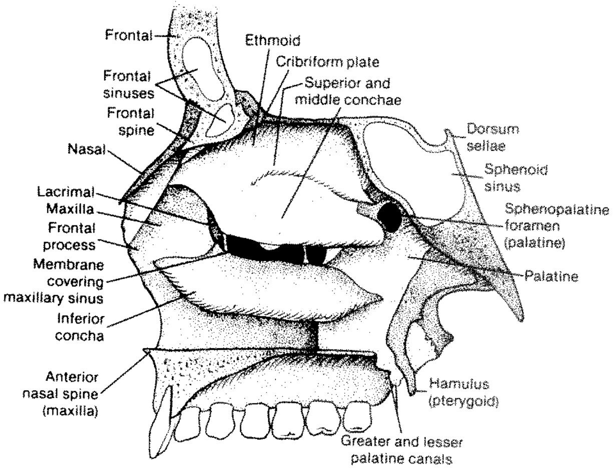
On the second postoperative day, Schirmer's test is performed to confirm that section of the nerve has been complete.

RESULTS

Twelve patients (five men and seven women) underwent bilateral endoscopic vidian neurectomy. Eight patients had secretomotor rhinopathy; four had recurrent nasal polyposis. The main operative difficulties encountered were 1) the narrow field of surgery in the first two cases and 2) bleeding as the posterior end of the middle turbinate was sectioned in the third case. The bleeding was stopped by suction coagulation. With regard to the narrow surgical field encountered initially, subsequent patients underwent lateral fracture of the posterior end of the middle turbinates. This procedure improved surgical visualization and manipulation (see Table).

All patients had immediate postoperative discomfort with dryness of the nose and nasal encrustation. Alkaline nasal lotion was given for 2 weeks to relieve this discomfort.

In spite of reduced lacrimation in all the patients, as proved by Schirmer's test, only three patients had irritation and redness of their eyes. All three patients had symptomatic relief with the use of tear substitutes. None had keratitis.


Frontal
Frontal sinuses
Frontal spine
Nasal
Lacrimal
Maxilla
Frontal process
Membrane covering maxillary sinus
Inferior concha
Anterior nasal spine (maxilla)
Ethmoid
Cribriform plate
Superior and middle conchae
Dorsum sellae
Sphenoid sinus
Sphenopalatine foramen (palatine)
Palatine
Hamulus (pterygoid)
Greater and lesser palatine canals

Bones of lateral wall of nasal cavity.

Fig 2. Lateral nasal wall. (Reprinted with permission from Cummings CW, Fredrickson JM, Harker LA, Krause CJ, Schuller DE. Otolaryngology–head and neck surgery. Part 1. St Louis, Mo: CV Mosby, 1986:516.)

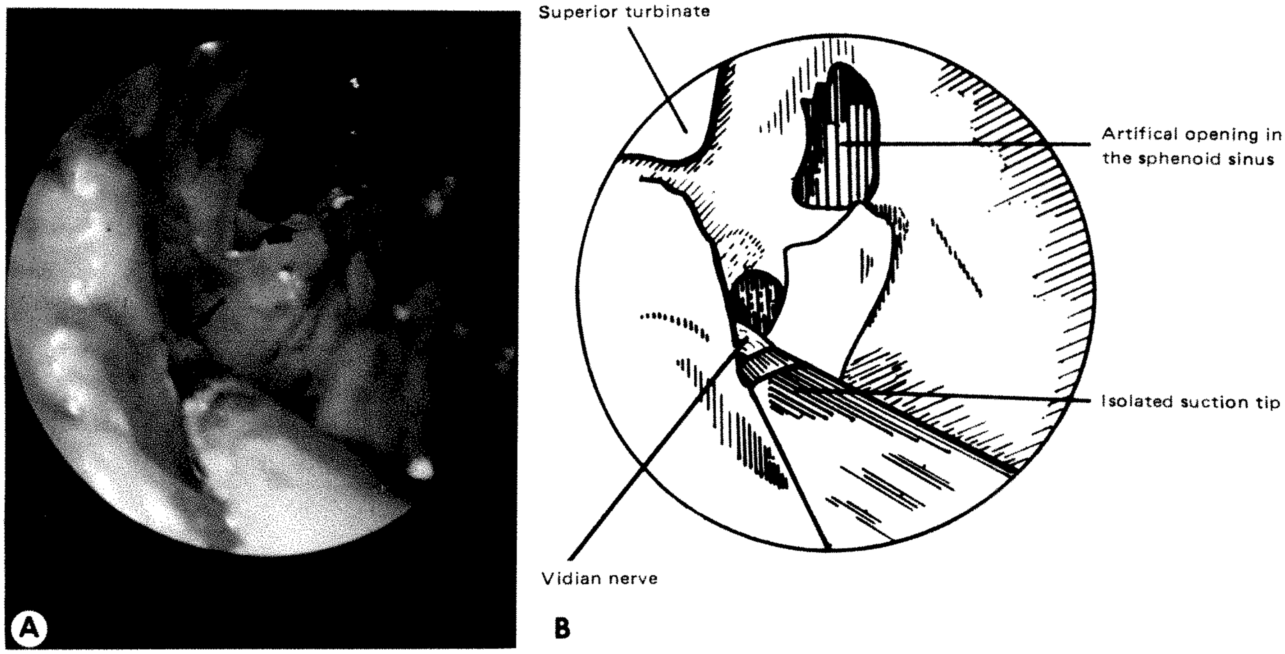


Fig 3. Stump of vidian nerve (long arrow on A) coming out of pterygoid canal. Shows artificial opening into sphenoid sinus (short arrow on A).

Two years of follow-up has revealed no recurrence of the nasal polyps in the four cases. Only one of the eight patients with secretomotor rhinopathy had recurrence of his symptoms. No long-term eye complications have occurred.

DISCUSSION

The efficacy of vidian neurectomy in relieving the symptoms of vasomotor rhinitis, such as sneezing and rhinorrhea, has been established by many workers. Ogale et al[9] in 1988 gave a success rate of 92% with chronic vasomotor rhinitis.

The technique of endoscopic surgery described herein is an attempt to overcome the drawbacks of previously described techniques. Difficulties with the transantral vidian neurectomy include extensive dissection through the pterygopalatine fossa, a long postoperative convalescence, and the possibility of persistent infraorbital neuralgia. Endoscopic surgery is a trial to further develop the microscopic transnasal vidian neurectomy technique, which does not allow the angled vision of the 30° telescope. Nasal endoscopy allows localization of the sphenopalatine foramen above the middle turbinate, where the vessels of the lateral nasal wall converge. Advancing the endoscope into the nose allows manipulation in the posterior part of the nasal cavity, even in the presence of moderate deviation of the nasal septum. The incision made along the relatively avascular posterior lip of the foramen minimizes the intraoperative bleeding. Curetting the thinner posterior and inferior lips of the foramen allows a wider operative field and close inspec-

OPERATIVE DIFFICULTIES OF ENDOSCOPIC VIDIAN NEURECTOMY

Case No.	*Sex*	*Diagnosis*	*Adjuvant Procedures*	*Intraoperative Difficulties*	*Early Postoperative Complications*
1	M	Secretomotor rhinitis		Narrow field	
2	M	Secretomotor rhinitis		Narrow field	
3	F	Secretomotor rhinitis	Removal of posterior end of middle turbinate on one side	Bleeding	Intranasal crusting
4	F	Recurrent nasal polyposis (3 times)	Polypectomy + intranasal ethmoidectomy		
5	M	Secretomotor rhinitis	Lateral fracture of middle turbinate		
6	F	Recurrent nasal polyposis (2 times)	Polypectomy + intranasal ethmoidectomy		
7	M	Recurrent nasal polyposis (2 times)	Polypectomy + intranasal ethmoidectomy		
8	F	Secretomotor rhinitis	Lateral fracture of middle turbinate		
9	F	Secretomotor rhinitis	Lateral fracture of middle turbinate		
10	M	Recurrent nasal polyposis (2 times)	Polypectomy + intranasal ethmoidectomy		
11	F	Secretomotor rhinitis	Lateral fracture of middle turbinate		
12	F	Secretomotor rhinitis	Lateral fracture of middle turbinate		

tion of the mouth of the pterygoid canal.

Two main difficulties were encountered: bleeding and working in a relatively narrow operative field. The first problem was avoided by using a hypotensive technique, the sucker dissector, and the coagulating suction tip. Concerning the narrow operative field, outfracture of the posterior end of the middle turbinate allowed good visualization without the need for resection of the posterior end of the middle turbinate. This procedure may, however, disturb the anatomy and invite more bleeding, as happened in the third case. All patients had uncomplicated postoperative courses owing to minimal manipulation within the nose. Nasal dryness and crusting were seen mainly in the third case and were due to turbinectomy. Eye symptoms, which occurred in three cases, improved with the use of tear substitutes. All of the female patients complained postoperatively of a lack of tears under emotional circumstances. Recurrence of symptoms in one case of secretomotor rhinopathy may have been due to regeneration of the nerve or incomplete section of the nerve.

These results demonstrate that endoscopic vidian neurectomy is a minor, relatively safe technique for a moderate otolaryngologic problem.

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TOXIC SHOCK SYNDROME ASSOCIATED WITH PHARYNGITIS AND SUBMANDIBULAR SPACE ABSCESS

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LCDR PATRICK J. GOMEZ, MC, USNR
PORTSMOUTH, VIRGINIA

Toxic shock syndrome continues to be encountered more frequently with the head and neck areas as sources of the toxin. In head and neck surgery practice it is most commonly noted following nasal packing. An unusual case associated with staphylococcal pharyngitis and spontaneous submandibular space abscess is reported and the literature concerning the subject is reviewed. Treatment is eradication of the infective focus, aggressive support of vital functions, and parenteral antistaphylococcal antibiotics.

KEY WORDS — staphylococcal pharyngitis, submandibular space abscess, toxic shock syndrome.

Toxic shock syndrome (TSS) is an acute multisystem disease with variegated features that has been known to exist for many years. It gained mass media attention when it became associated with young healthy menstruating women using tampons. Lately, the syndrome has been reported with increasing frequency in the head and neck surgery literature. It is becoming obvious that every medical and surgical specialty may encounter this problem and it is wise for all physicians to be well versed in the features of this disorder.

CASE REPORT

A 22-year-old man was evaluated in the emergency room stating a 4-day history of sore throat and low-grade fever. A throat culture was obtained, pharyngitis was diagnosed, and he was prescribed penicillin V potassium. He returned to the emergency room 24 hours later complaining of a pruritic, generalized, erythematous skin rash that was believed to be from penicillin sensitivity. The penicillin was discontinued and erythromycin ethylsuccinate and Benadryl were instituted. The patient returned to the emergency room 2 days later stating a 24-hour history of lethargy, fever, chills, nausea, vomiting, left-sided neck pain, and increasing odynophagia. He denied any history of dysphagia, shortness of breath, or stridor. The results of the physical examination revealed a somnolent male who appeared quite weak and had a temperature of 39.6°C orally. His blood pressure was 96/40 supine and 60/40 sitting. His apical heart rate was 120 beats per minute. His conjunctivae were markedly injected, but the funduscopic examination findings were normal. A "strawberry tongue" was noted with prominent, erythematous papillae (Fig 1). Findings on a flexible fiberoptic examination of the larynx were unremarkable. There was a 6 x 6-cm tender fullness in the left submandibular region. No other masses were palpable. There was a diffuse erythematous rash sparing the palms and soles. Laboratory evaluation revealed a white blood cell count of 17.1, a prothrombin time of 13.3, and a partial thromboplastin time of 43.9. His liver enzyme levels each exhibited a mild elevation (serum glutamic-oxaloacetic transaminase, serum glutamate pyruvate transaminase, lactate dehydrogenase, and alkaline phosphatase). A specific gravity of 1.021 and 2+ ketones were noted on urinalysis. His throat culture specimen, which was obtained 3 days

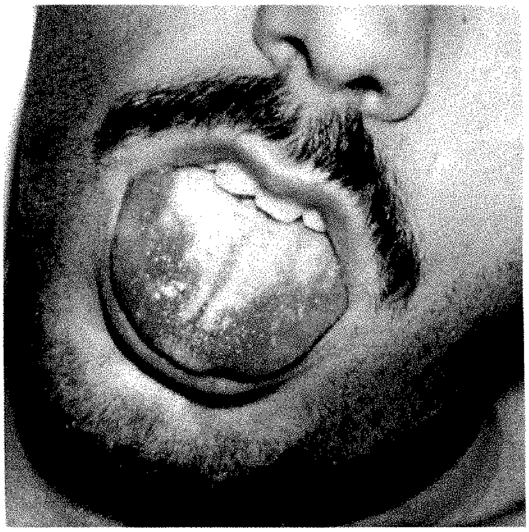

Fig 1. "Strawberry tongue" in patient with toxic shock syndrome.

From the Department of Otolaryngology–Head and Neck Surgery, Naval Hospital, Portsmouth, Virginia (all authors), the Department of Otolaryngology–Head and Neck Surgery, Eastern Virginia Medical School, Norfolk, Virginia (Galantich, Kennedy), and the Department of Surgery, F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland (Galantich, Kennedy). The work reported herein was partly performed under the United States Navy Clinical Investigation Program, report number 90-08-1969-85. The opinions or assertions expressed herein are those of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy or the Department of Defense.

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REPRINTS — LCDR Peter T. Galantich, MC, USNR, Dept of Otolaryngology–Head and Neck Surgery, Naval Hospital, Portsmouth, VA 23708-5100.

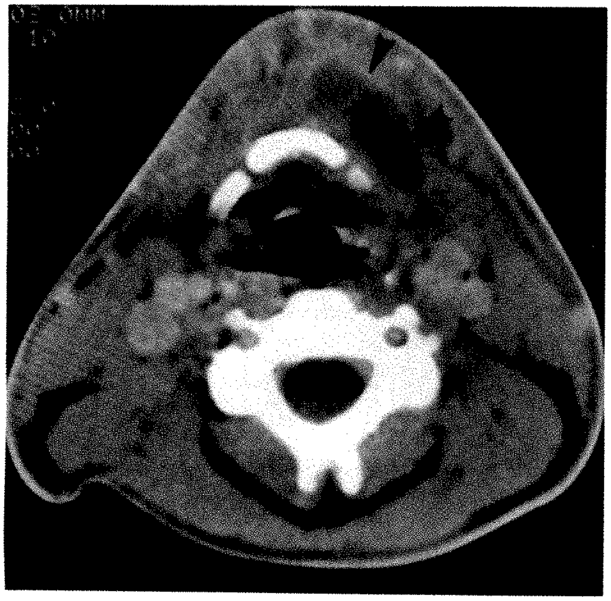

Fig 2. Computed tomogram of neck indicating hypodense area (arrowheads) in anterior left submandibular area consistent with abscess formation.

prior to admission, was positive for *Staphylococcus aureus*. The patient received 8 L of lactated Ringer's solution prior to stabilization of his blood pressure in the emergency room. A computed tomography scan of the neck revealed a hypodense area in the left anterior submandibular space consistent with the fluid of abscess formation (Fig 2).

Intravenous clindamycin hydrochloride and vancomycin hydrochloride were started and the left submandibular space abscess was incised and drained. The patient was observed in the intensive care unit for 48 hours without any further sign of cardiovascular instability. An infectious disease consultation was obtained on admission and the consultants concurred with the diagnosis of TSS. A 10-day course of intravenous antistaphylococcal antibiotics was recommended. The patient's cultures from the operative site resulted in a heavy growth of *S aureus* that was sensitive to methicillin. Since the rash previously attributed to possible penicillin allergy was felt to be secondary to TSS, the antibiotics were then changed to oxacillin to complete his intravenous antibiotic treatment. He was discharged on his 10th hospital day and prescribed 14 days of oral dicloxacillin sodium. Four days after his discharge, the patient developed a desquamating skin rash on the palms of his hands that resolved without additional treatment. The patient returned to work 10 days after being discharged from the hospital.

COMMENT

The earliest description of TSS came in 1927 by Franklin Stevens,[1] who reported two patients with staphylococcal-induced pharyngitis associated with what appeared to be scarlet fever. About 50 years later, Todd and Fishaut[2] coined the term "toxic shock syndrome" to describe a constellation of signs and symptoms seen in seven pediatric patients ranging from 8 to 17 years of age. These children presented with high fever, headache, confusion, conjunctival hyperemia, a scarlatiniform rash, subcutaneous edema, vomiting, diarrhea, oliguria, and signs of multiorgan failure that were followed by desquamation of the palms and soles. Todd and Fishaut noted the association was between this disease and phage group 1 *S aureus* that produced an exotoxin.[2] Since these early descriptions, the criteria for diagnosis of TSS have been well delineated by the Centers for Disease Control. These guidelines include four major criteria (fever, rash, desquamation, and hypotension) and the association of other multisystem involvement (see Table[3]).

TOXIC SHOCK SYNDROME CASE DEFINITION

- Fever (temperature 38.9°C)
- Rash (diffuse macular erythroderma)
- Desquamation, 1 to 2 weeks after onset of illness, particularly of palms and soles
- Hypotension (systolic blood pressure <90 mm Hg for adults or <5th percentile by age for children <16 years of age, or orthostatic syncope)
- Involvement of three or more of the following organ systems
  - Gastrointestinal (vomiting or diarrhea at onset of illness)
  - Muscular (severe myalgia or creatine phosphokinase level >2x ULN)
  - Mucous membrane (vaginal, oropharyngeal, or conjunctival hyperemia)
  - Renal (blood urea nitrogen level or creatinine level >2x ULN or >5 white blood cells per high-power field — in absence of urinary tract infection)
  - Hepatic (total bilirubin, serum glutamic-oxaloacetic transaminase level, or serum glutamate pyruvate transaminase level >2x ULN)
  - Hematologic (platelets <100,000/mm^3)
  - Central nervous system (disorientation or changes in consciousness without focal neurologic signs when fever and hypotension are absent)
- Negative results on the following tests, if obtained
  - Blood, throat, or cerebrospinal fluid cultures
  - Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

Information from reference 3.

>2x ULN — twice upper limits of normal for laboratory.

The typical patient with TSS presents with a 1- to 4-day prodrome of fever, chills, malaise, and severe myalgias. This is often followed by nausea, vomiting, diarrhea, headache, sore throat, and orthostatic symptoms. The rash is present in all cases and by definition is usually described as a diffuse nonpruritic sunburnlike rash that blanches with pressure. The rash usually fades in 3 days and can easily be missed if it is not sought specifically. The skin normally desquamates 5 to 12 days after the initial rash has resolved in all patients who survive. The conjunctival and mucous membranes typically are described as injected and hyperemic and the tongue is often referred to as "strawberry" in appearance. The most common neurologic manifestation reported is headache. Other nonfocal abnormalities, such as confusion, disorientation, hallucination, and agitation, can be features.[4]

Nonmenstrual TSS is associated with the same clinical manifestations and etiologic agent as menstrual TSS. Initially, in 1980, when the majority of cases of TSS were being reported, nonmenstrual cases accounted for 7%. The percentage of nonmenstrual cases reported increased to 27% in 1984, primarily as the result of a reduction in reporting of menstrual-related cases.[5] The most commonly reported cases of nonmenstrual TSS in the head and neck literature appear to be in postoperative patients, especially after nasal surgery. The interval between operation and the onset of TSS symptoms has often been reported as less than 24 hours, but more typically is 2 days. In most of these postoperative wound infections the actual surgical site appears minimally inflamed without obvious signs of suppuration.[6] The incidence of TSS after nasal surgery is quite rare, but Jacobson and Kasworm[7] reported in Utah for the years 1980 to 1983 a rate of 16.5 per 100,000, which was higher than the incidence of TSS in women of menstrual age.

Presently, there is no definitive test for TSS, so the diagnosis has to be made by clinical criteria. The differential diagnosis of TSS includes staphylococcal scalded skin syndrome, streptococcal scarlet fever, Kawasaki's disease, Rocky Mountain spotted fever, and leptospirosis. The first three listed in this differential are predominately diseases of children and do not present with detectable hypotension. The rash in TSS also differs from those of Kawasaki's disease, Rocky Mountain spotted fever, and leptospirosis, which are usually maculopapular or petechial rashes. Kawasaki's disease also may present with significant lymph node enlargement, which is not usually found in TSS.[5]

Our patient presented with four of the major criteria for TSS along with evidence of mucous membrane, gastrointestinal, and mild liver involvement. *Staphylococcus aureus* was grown from both the pharynx and the submandibular space abscess. His blood and urine cultures were negative for growth of microorganisms. The lack of positive blood cultures and urine cultures is typical for TSS. No gram-negative bacteria were noted on Gram stain or cultures, as noted in some other TSS reports.[5] The presentation of TSS in S *aureus* pharyngitis is not uncommon, and on review of some of the larger series, TSS staphylococcal pharyngitis has been found to be present in 55% to 100% of the patients.[8] Our patient was unusual in that he presented with a spontaneous submandibular space abscess, which is rare in TSS. This focus of S *aureus* could be considered to be analogous to the foreign body–containing focus of S *aureus* that has been noted in many of the previous TSS reports.[6] The presence of this documented focus of S *aureus* and the inclusion of the majority of the TSS case definition criteria (see Table) in the patient's clinical presentation strongly support the diagnosis.

The treatment of patients with TSS is mainly supportive and the mainstay of therapy is removal of any source of infection to prevent any further formation of exotoxin. Possible sources include tampons, nasal splints or packing, abscesses, and surgical wounds. Hypotension is aggressively treated with vigorous crystalloid fluid resuscitation. Close intensive care unit monitoring is required until the patient's hemodynamic status is stabilized. Vasopressors are occasionally used in patients who are unresponsive to fluid resuscitation. The clinical syndrome is the result of circulating exotoxins, which are not thought to be affected by antibiotic therapy, although most authors recommend treatment with a β-lactamase–resistant penicillin (nafcillin or oxacillin), first-generation cephalosporins, clindamycin, or vancomycin.[9]

CONCLUSION

Toxic shock syndrome continues to be a rare cause of life-threatening shock. It most commonly results from the colonization of tampons in menstruating women. As the mechanism of the disease has become more evident, the incidence of postmenstrual TSS has decreased dramatically. However, the reported incidence of TSS in nonmenstrual cases has risen steadily. We present an unusual case of TSS in a 22-year-old man who presented with pharyngitis and submandibular space abscess. Frequently prescribed antibiotics adequately cover streptococcal infections; however, this leaves the S *aureus* infections untreated. We suggest aggressive management of persistent pharyngitis with throat cultures and appropriate antibiotic treatment based on sensitivity results.

ACKNOWLEDGMENT — The authors thank Mary Anne Centonze for editorial assistance.

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FIRST INTERNATIONAL LARYNGOTRACHEAL RECONSTRUCTION SYMPOSIUM

The Cleveland Clinic Foundation is sponsoring a continuing education program entitled First International Laryngotracheal Reconstruction Symposium. The symposium will be held August 24-27, 1991, at Stouffer Tower City Plaza Hotel in Cleveland, Ohio. For further information, please contact The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Rm TT-31, Cleveland, OH 44195-5241; 444-5696 (local) or (800) 762-8173.

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INTERNATIONAL SYMPOSIUM ON GRAVES' OPHTHALMOPATHY

An International Symposium on Graves' Ophthalmopathy will be held Aug 23-24, 1991, in Amsterdam, the Netherlands. The symposium will bring together members from different disciplines interested in the management of Graves' ophthalmopathy. The program will include lectures, free communications, and posters on topics on surgical, medical, and radiotherapeutic management, on immunological aspects, and on classification of the eye changes. The deadline for submission of abstracts is June 1, 1991. For further information, contact Amsterdam Thyroid Club, c/o W. M. Wiersinga, MD, Dept of Endocrinology, F5-258, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.

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NASOPHARYNGEAL CARCINOMA: MODES OF PRESENTATION

DEREK W. SKINNER, FRCS
SHREWSBURY, ENGLAND

C. ANDREW VAN HASSELT, MMED(OTOL), FCS(SA)
HONG KONG

S. Y. TSAO, DMRT, FRCR
HONG KONG

Nasopharyngeal carcinoma (NPC) is a common malignancy among the southern Chinese people and has a poor prognosis. The aim of this study was to describe in detail the presentation of NPC as found between 1984 and 1988 at Prince of Wales Hospital, Hong Kong. Our study confirmed that patients present with an advanced stage of malignancy; 70% were stage III to V. Eighty-two percent of patients were between 21 and 60 years of age. The symptoms often suggested benign disease and most patients would delay seeking treatment for at least 5 months. We recommend inspection of the nasopharynx with flexible nasoendoscopy for all persons in high-risk areas on a regular basis and advise a policy of active health education for both physicians and the general population to reduce the stage of NPC at first presentation.

KEY WORDS — early detection, nasopharyngeal carcinoma, presentation.

INTRODUCTION

In Hong Kong, nasopharyngeal carcinoma (NPC) forms the third commonest malignant tumor to present in males and sixth commonest tumor in females.[1] During 1984, 1,032 new cases presented to all hospitals in Hong Kong, and during 1987, 15.5 persons per 100,000 of the Hong Kong population died of NPC.[1] The Hong Kong incidence may appear low when compared with that of the Tumor Hospital of Chungshan Medical College in Guangzhou, Guangdong Province, People's Republic of China, in which almost 3,000 new cases of NPC are seen each year for treatment (unpublished data).

The prognosis for patients presenting with NPC is poor because of the advanced stage of the disease at presentation. The 5-year actuarial survival as noted by Ho[2] is 83.7% for stage I, 67.9% for stage II, 40.3% for stage III, and 22.3% for stage IV. If patients could be treated when the disease is in stage I or II, rather than more advanced, then their prognosis would be much better. The reason for this late presentation of NPC is at least twofold. Delay in seeking medical advice by the patient[3] and the nature of the presenting symptoms, which are subtle and often confusing to the unwary clinician, almost certainly account for late diagnosis and subsequent delay in treatment of patients.

The aim of this paper was to analyze in detail the presentation of NPC in a high-risk region (Hong Kong) and examine the correlations between sex, age, and other factors on the stage of presentation of the disease. The data on 437 patients presenting to Prince of Wales Hospital, Hong Kong, from July 1984 to December 1988 were gathered prospectively. All patients presented primarily to medical and surgical departments within this hospital and histologic diagnosis was confirmed by the same pathologists. Subsequent treatment was also carried out by the appropriate departments within this hospital.

MATERIALS AND METHODS

Between July 1984 and December 1988 over 1,000 patients were treated for NPC at Prince of Wales Hospital, Hong Kong. Four hundred thirty-seven patients presented new cases without previous diagnosis and thus were investigated and histologically assessed within this institution from the outset. These patients were confirmed as having either nonkeratinizing or anaplastic squamous cell carcinoma according to the World Health Organization (WHO) classification,[4] types 2 and 3 respectively, by the same pathologists. Five cases of keratinizing squamous cell carcinoma (WHO type 1) were found but have not been included in this analysis. The remaining patients not studied in this series had their NPC treated at Prince of Wales Hospital but had been investigated, staged, and histologically diagnosed at several different hospitals and were referred for treatment alone. These patients have not been included in this study.

Details concerning the patients' age, sex, duration of presenting complaint, nature of presenting complaint, nature of all other associated complaints, presence of cranial nerve involvement, trismus, cervical lymphadenopathy, site of primary in the nasopharynx, presence of secretory otitis media, staging details, death, family history, and presence of other neoplasms and distant metastases were collected prospectively and further analyzed.

From the Departments of Surgery (Otorhinolaryngology) (Skinner, Van Hasselt) and Clinical Oncology (Tsao), The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong. Dr Skinner is now at the Department of Otolaryngology–Head and Neck Surgery, Eye, Ear & Throat Hospital, Murivance, Shrewsbury SY1 1JS, England.

REPRINTS — C. Andrew Van Hasselt, MMED (Otol), Dept of Surgery, Prince of Wales Hospital, Hong Kong.

TABLE 1. HO STAGING SYSTEM FOR NASOPHARYNGEAL CARCINOMA

T stage	
T1	Confined to nasopharynx
T2	Tumor extends to nasal fossa, adjacent muscles of oropharynx, or nerves below skull base
T3	Extension beyond areas of T1 and T2
T3a	Bone involvement below skull (including sphenoid floor)
T3b	Involvement of skull base
T3c	Cranial nerve involvement
T3d	Involvement of orbits, laryngopharynx, or infratemporal fossa
N stage	
N0	No nodes evident
N1	Nodes entirely within upper cervical level
N2	Nodes palpable between upper cervical level lower boundary and supraclavicular fossa
N3	Nodes palpable in supraclavicular fossa and/or skin involvement (cancer en cuirasse)
M stage	
M0	No evidence of distant metastases
M1	Definite evidence of distant metastases

Information from Ho.[5]

The presenting complaint was defined as the main complaint that caused the patient to seek medical advice. This study has also analyzed all the other symptoms found in each patient, which were often discovered after direct questioning. These are described for analytical purposes as "all complaints" (includes the presenting complaint). The minimum unit of time used throughout the study was 1 month; thus, durations of time less than 4 weeks have been rounded up to equal 1 month.

In this study the staging system used is that described by Ho in 1978 (Tables 1[5] and 2[5]). This system is used throughout Hong Kong and the AJC and UICC staging systems have not been considered.

The statistical tests used throughout this study include the unpaired Student's t test and χ^2 tests; p values of .05 or better have been regarded as statistically significant.

TABLE 2. STAGE GROUPING (HO SYSTEM)

	T1	*T2*	*T3*
N0	I	II	III
N1	II	II	III
N2	III	III	III
N3	IV	IV	IV
M1 = V			

Information from Ho.[5]

RESULTS

Race. All patients studied were born in Hong Kong, Macau, or the southern provinces of the People's Republic of China and resided in Hong Kong.

Sex. In this study 313 males and 111 females were found (3 unrecorded), with a male to female ratio of 2.8 to 1.

Age. Figure 1 illustrates the age and sex distribution for the patients presenting with NPC. The mean age for all patients at presentation was 47.3 years (SD, 13.27). For males the mean was 48.2 years and for females 44.5 years (range, 14 to 81 years). There was no significant difference between the age distribution of the males and females. In comparing stages I to V the age at presentation was found to increase with the advancing disease stage. The mean age ranged from 40.8 years for stage I to 54.1 years for stage V ($p \leq .05$ or better between stages).

Presenting Complaint. Table 3 summarizes the frequency of occurrence of each presenting complaint. The mean duration of the presenting complaint at the time of presentation for investigation and treatment was 4.7 months (SD, 4.73; range, 1 to 30 months), with no significant difference found between the sexes. Figure 2 shows the distribution of the duration of the presenting complaint. It can be seen that 56% present within the first 3 months of onset, 80% present within 6 months of onset, and 94% within 12 months of onset. Patients with stage V disease were found to present significantly later than those with stages I to IV ($p \leq .05$), the mean duration of the presenting complaint at presenta-

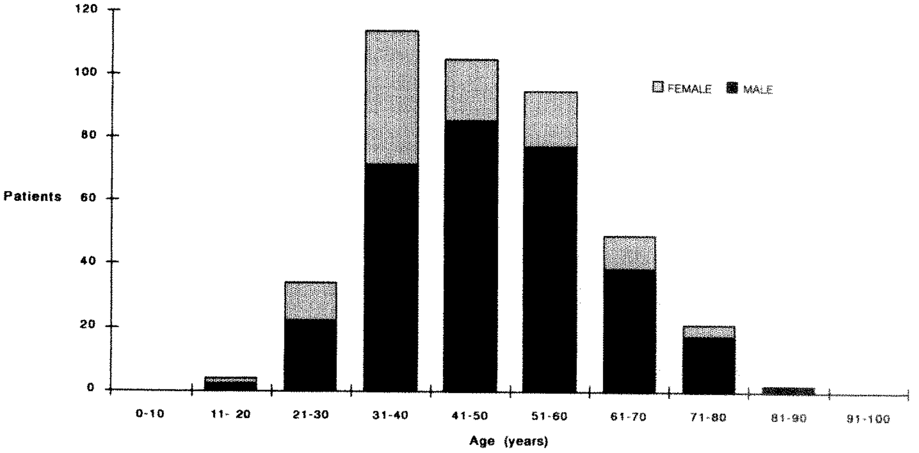

Fig 1. Age distribution for males and females with nasopharyngeal carcinoma.

TABLE 3. DISTRIBUTION OF PRESENTING COMPLAINTS

Complaint	*Patients*	
	No.	*%*
Neck mass	180	43.2
Unilateral	149	35.8
Bilateral	28	6.7
Contralateral	3	0.7
Aural	72	17.3
Unilateral deafness	50	12.0
Bilateral deafness	5	1.2
Otalgia	3	0.7
Otorrhea	2	0.4
Tinnitus	12	2.8
Nasal	128	30.7
Blood-stained discharge	77	18.5
Moderate to severe epistaxis	1	0.2
Nasal discomfort	0	0
Unilateral obstruction	22	5.2
Bilateral obstruction	19	4.5
Postnasal drip	9	2.1
Miscellaneous symptoms	36	8.6
Facial paresthesias	2	0.4
Facial palsy	0	0
Throat pain	6	1.4
Hoarseness	3	0.7
Dysphagia	0	0
Shoulder weakness	0	0
Tongue changes	0	0
Blindness	1	0.2
Headache	19	4.5
Trismus	0	0
Vertigo	0	0
Diplopia	5	1.2
Symptoms from distant metastases	5	1.2

tion being 4.5 months for stages I to IV and 6.5 months for stage V.

The five patients with the presenting symptom related to the distant metastases included one with abdominal pain from liver capsule infiltration, one with hip pain and two with back pain from bone involvement, and one patient with hypopituitarism from sphenoid sinus and subsequent dural infiltration. One further case was discovered as an incidental finding in the investigation for an unrelated illness and one other was discovered during the follow-up of other family members at risk for NPC.

All Complaints. Table 4 summarizes the frequency of all the complaints found in every patient with NPC and the duration of time they had been present prior to presentation. The symptoms described include the main presenting complaint and all the other symptoms they had related to their NPC.

Aural Signs. Otitis media with effusion (OME), identified by the appearance of the tympanic membrane and tympanometry, occurred unilaterally in 28% (120) of patients and bilaterally in 5% (21). Of all patients complaining of unilateral deafness 57% had unilateral OME and 29% had bilateral OME. Of patients with bilateral deafness 5% had unilateral OME and 42% had bilateral OME. One hundred twenty-four patients had unilateral deafness and 21 bilateral deafness at presentation. We compared deafness with the tympanic membrane signs of OME; 36% (51) of patients with OME did not complain of deafness and 39% (55) of patients who were deaf did not have evidence of OME. In comparison of the incidence of OME with stage of the NPC, the only significant differences in incidence were between stages II and III ($p \leq .02$) and stages III and IV ($p \leq .05$), with stage III demonstrating a higher incidence of OME (40.8% or 76 patients).

Neck Signs. Seventy-two percent (314) of patients had cervical lymphadenopathy at the time of presentation of their disease. Of those patients, 66.8% (210) had unilateral nodes and 33.1% (104) had bilateral nodes as found by the attending physician. When comparing the age distribution for the presentation of unilateral and bilateral nodes, we found no significant difference. It is interesting to note that only 239 patients had noticed a lump in the neck prior to admission (ie, 76% of those with N1 to N3).

Nasopharyngeal Findings. The appearance of the nasopharynx through either the flexible nasoendo-

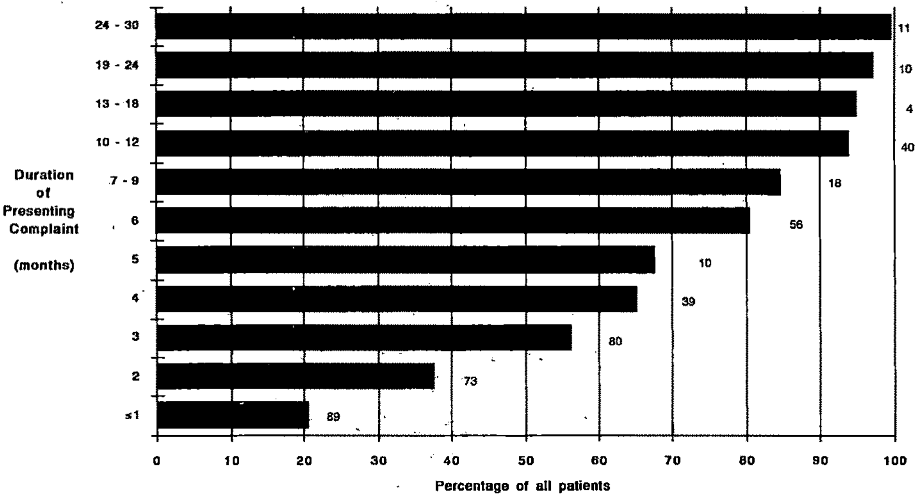

Fig 2. Proportion of patients who presented with regard to duration of presenting complaint. (Patient numbers are entered with each group.)

TABLE 4. DISTRIBUTION AND DURATION OF ALL COMPLAINTS

	Patients		Duration (mo)	
Complaint	*No.*	*%*	*Mean*	*Range*
Neck mass	239	57.6	4.16	1-36
Unilateral	196	47.2	4.29	1-36
Bilateral	40	9.6	3.67	1-24
Contralateral	3	0.7	2.66	1-4
Aural	178	42.9	4.53	1-24
Unilateral deafness	124	29.4	4.46	1-24
Bilateral deafness	21	5.0	5.04	1-24
Otalgia	13	3.1	3.50	1-12
Otorrhea	5	1.2	5.00	3-9
Tinnitus	121	29.1	4.58	1-24
Nasal	234	56.3	4.99	1-36
Blood-stained discharge	192	46.3	4.70	1-36
Moderate to severe epistaxis	1	0.2	2.00	2
Nasal discomfort	3	0.7	8.66	2-12
Unilateral obstruction	82	19.7	5.24	1-24
Bilateral obstruction	45	10.8	7.37	1-36
Postnasal drip	128	30.8	4.33	1-36
Miscellaneous symptoms	102	24.6	3.49	1-36
Facial paresthesias	22	5.3	3.50	1-12
Facial palsy	0	0	0	
Throat pain	16	3.8	3.12	1-12
Hoarseness	11	2.6	2.50	1-6
Dysphagia	10	2.4	1.70	1-3
Shoulder weakness	0		0	
Tongue changes	1	0.2	2.00	2
Blindness	5	0.2	2.40	1-4
Headache	75	18.0	4.69	1-36
Trismus	6	1.4	2.16	1-4
Vertigo	17	4.0	2.05	1-6
Diplopia	16	3.8	2.43	1-6
Symptoms from distant metastases	5	1.2		

scope or the rigid 90° Hopkins rod telescope with a soft palate retractor conformed to that of either an ulcerative lesion or a smooth submucosal bulge. It was found that 82% (342) of the NPCs were lateral in origin; they were exactly equal in number on the right and left. Twelve percent (51) were found to be central in origin and 6% (24) left a normal appearance to the nasopharynx. In 20 cases it was not possible to adequately estimate the origin because of the size of tumor bulk. These appearances were confirmed by computed tomographic scanning. It is interesting to note that 3 of the patients with a normal nasopharyngeal appearance had cranial nerve palsies. The T stage distribution for patients with a normal appearance to the nasopharynx at endoscopy included 8 with T1, 11 with T2, and 5 with T3 tumors. When the NPC was found to be centrally placed the incidence of bilateral cervical lymphadenopathy was significantly greater ($p \leq .02$) than for a laterally placed primary tumor. A laterally placed NPC did not have a significantly higher incidence of unilateral cervical lymphadenopathy in comparison to the centrally placed primary tumors.

Cranial Nerve Palsy. Fifty-two (12%) patients were found with cranial nerve palsies; 28 had a single nerve palsy, 24 had multiple palsies, and 14 (3%) patients had Horner's syndrome at presentation. Figure 3 illustrates the distribution of the nerves affected. The nerve most commonly affected was the maxillary division of the trigeminal nerve. In consideration of the position of the NPC in the nasopharynx there was no significant difference between a lateral wall tumor, a centrally placed tumor, or a normal-appearing nasopharynx with regard to the incidence of cranial nerve palsy. There was no significant difference between N0 and N1-3 in the incidence of cranial nerve palsy.

Stage at Presentation. The Ho staging system[5] is used throughout and results are shown in Figs 4 and 5. There was no significant difference ($p \leq .1$) be-

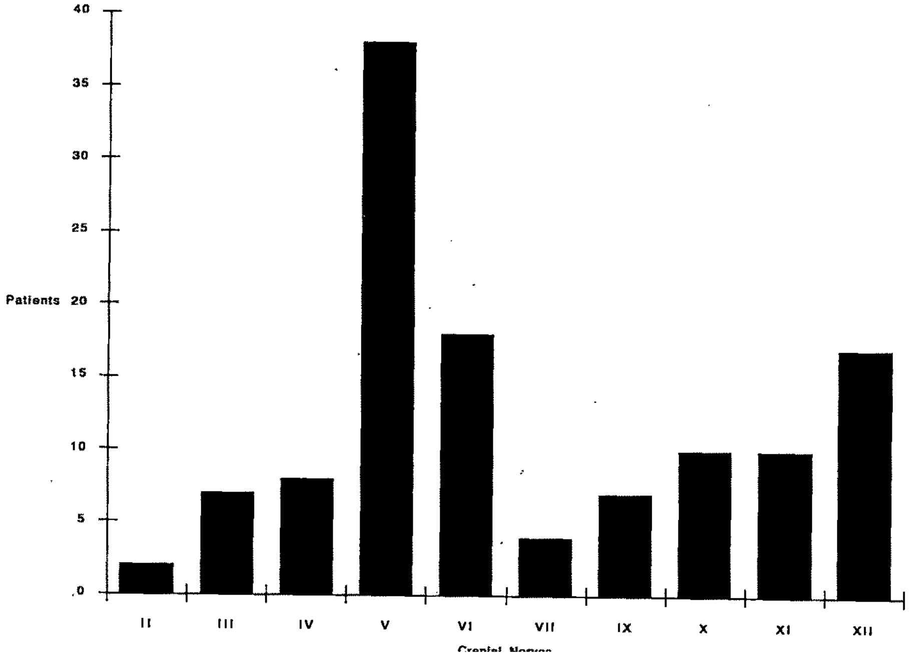

Fig 3. Distribution of cranial nerve involvement.

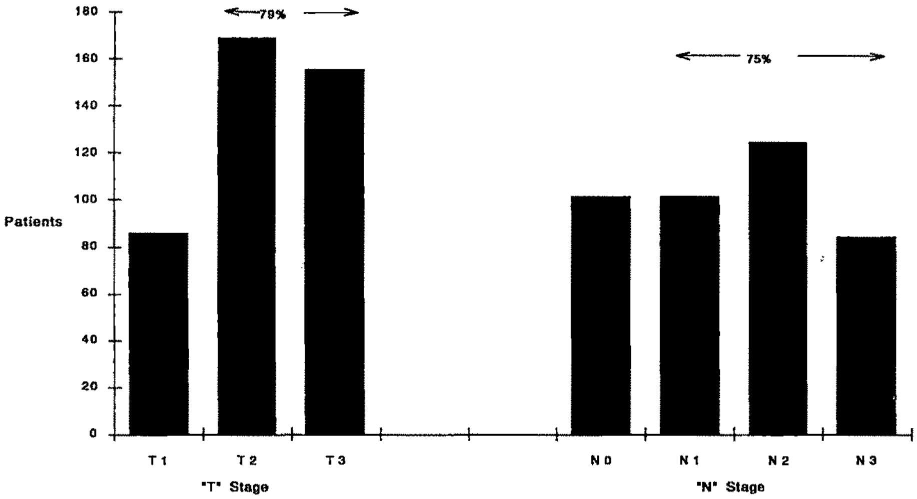

Fig 4. Frequency distribution for T and N stage for nasopharyngeal carcinoma.

tween the sexes in the distribution of the stage of disease at presentation.

Distant Metastases. Nineteen patients (4.6%) had evidence of distant metastases at presentation — 4 patients with multiorgan involvement. The commonest site was bone (13 patients), followed by lung (6) and liver (5). The mean age at presentation of patients with distant metastases (54 years) was significantly greater ($p \leq .025$) than those without (46.8 years). Metastases were found at more than one site in 4 patients. In 5 patients the distant metastases were the presenting complaint.

Family History. Nineteen (4.3%) patients had a first- or second-degree relative with NPC. Four had a father with NPC, two a mother, five a brother, and three a sister. The male predominance of the condition is reflected in the family incidence.

Second Malignant Neoplasm. Six (1.3%) patients had other, apparently unrelated neoplasms including adenocarcinoma of the rectum, squamous cell carcinoma of the larynx, non-Hodgkin's lymphoma, carcinoma of the breast, and (in two cases) adenocarcinomas of the stomach. No other Epstein-Barr virus-related tumors were noted in patients with NPC.

DISCUSSION

This study confirms that Hong Kong NPC patients have consistently maintained a similar male to female ratio, 2.8 to 1, into the mid-1980s despite a reduction in the incidence of NPC.[6] This ratio varies very little throughout the world, yet the significance of male predominance is unclear.[7,8] Females are known to have a slightly better survival rate after treatment[9] and it is known that concurrent pregnancy or pregnancy within 1 year of treatment will result in a very poor prognosis.[10]

The age distribution found in our study concurs with other reports of Chinese patients.[11,12] In the Chinese, NPC affects the younger age groups, with 60% of patients in this study under the age of 50 years and only 16% over the age of 70 years. No children under the age of 14 years were found. In non-Chinese studies NPC occurs predominantly in the fifth, sixth, and seventh decades.[7,9]

It may seem encouraging that 80% of patients were found to present within 6 months of becoming aware of their symptoms and only 6% presented after 12 months. This compares very favorably with other reports that found the duration of symptoms to be longer.[9,13,14] Despite this, 70% of all patients

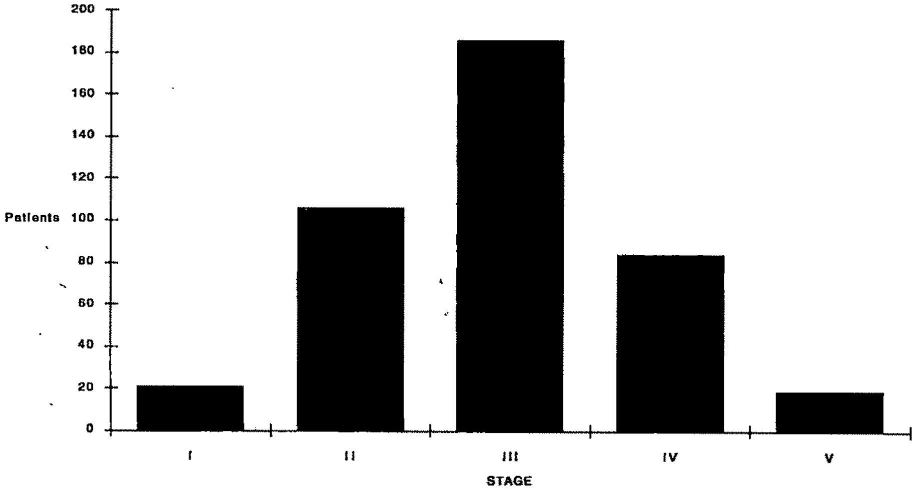

Fig 5. Frequency distribution for stage grouping for nasopharyngeal carcinoma.

presented with an advanced stage of the disease, ie, stage III to V. The exact cause for delay in the diagnosis of NPC was not fully examined in this particular study, but in an earlier study from this institution[15] it was found that trivialization of symptoms by both the patients and the attending physicians was the main source of the delay.

The most common presenting complaint found was a unilateral neck mass, followed by nasal symptoms and aural symptoms. Nasal complaints were almost as common as the awareness of a mass in the neck. A blood-stained nasal discharge was found in almost 50% of patients and had been present for almost 5 months before a diagnosis had been made. Ten percent of patients had significant bilateral nasal obstruction for more than 7 months before seeking medical advice. This high frequency of nasal complaint in NPC has not been noted before, and if such patients had presented with these symptoms much earlier, eg, within 1 or 2 months, then the prognosis following treatment would have been much better. A similar problem is seen with the patients with aural symptoms, including deafness present for 4 to 5 months and tinnitus present for more than 4 months.

The symptoms that caused most discomfort, eg, hoarseness, dysphagia, blindness, trismus, vertigo, and diplopia, presented significantly sooner (mean, <3 months) than the symptoms that were more insidious, eg, deafness and nasal obstruction (mean, >4.5 months; $p \leq .005$). Many of the symptoms of NPC may be misconstrued as those of benign disease. This problem was seen with headache, a relatively common symptom (18%) that may be disregarded in its early stages in some patients. Postnasal drip was found to be a common nasal symptom (30.8%), as was nasal obstruction (30%), yet both these symptoms are common features of benign nasal disease and if the clinician is not suspicious they may be initially treated as rhinitis. Adequate examination of the nasopharynx is essential, as 21% of patients had a small T1 lesion and 6% had normal findings on fiberoptic nasoendoscopy despite the presence of tumor that was revealed histologically.

The mean duration of ipsilateral cervical lymphadenopathy was 4.29 months and that of bilateral cervical lymphadenopathy was 3.67 months. There was no significant difference between these durations; thus, it would seem that bilateral nodes occur simultaneously on each side and not because of an increased time duration before presentation. Fifty-seven percent of patients were aware of a neck mass at presentation and had been aware of its presence for more than 4 months. On clinical examination 75% of patients were found to have N1 to N3 disease on staging; thus, almost 20% of patients were unaware of a mass within the neck at the time of diagnosis. It is possible that teaching the general population in a high-risk country like Hong Kong to examine their own necks regularly may help to reduce the N stage at presentation and thus improve the prognosis. The relationship of a centrally placed NPC within the nasopharynx and the significantly higher incidence of bilateral lymphadenopathy in this group has not previously been demonstrated. This finding supports the argument for irradiating both sides of the neck in any patient with a central NPC and only unilateral lymphadenopathy at presentation.

Deafness was a common symptom in this study (35%) yet accounted for only 13% of the *presenting* complaints. Several other studies[7,9,16] found that 25% to 40% of patients presented with aural symptoms and it may be that the differentiation between *presenting* and *all* complaints found in our study accounts for the difference in incidence. Of the 35% of patients with deafness at presentation, 62% were found to have either unilateral or bilateral OME. The remaining deaf patients without OME may be accounted for in two ways. First, the age of the patients with NPC ranges into the age group for development of presbycusis, which would produce a sensorineural hearing loss and no middle ear effusion. It is likely that the patients with bilateral deafness had a higher incidence of presbycusis-related hearing loss, as only 47% of such patients had OME. Second, OME is known to be a fluctuating problem in the presence of adenoidal hypertrophy,[17] and this characteristic may also pertain to NPC. Su and Juan[18] have shown that the eustachian tube dysfunction found in NPC is functional in nature and not mechanical, and this finding would support the possibility that the OME is a fluctuating phenomenon and thus not always demonstrated at the time of presentation despite the complaint of deafness. Thirty-six percent of patients had OME at presentation yet did not notice any deafness; this finding confirms the fact that adequate examination of the tympanic membranes and tympanometry should be conducted in every patient with NPC as a method of assessing eustachian tube involvement.

Patients with cranial nerve palsies presented soon after they became symptomatic (mean, 2.6 months) — significantly earlier than the patients presenting with ear, nose, or neck symptoms ($p \leq .005$) — presumably because of the severity of the problems arising from such palsies, eg, hoarseness, dysphagia, blindness, and facial paresthesias. The incidence of cranial nerve palsy (12%) in this study was less than that found by Neel,[16] who found that almost 20% of patients had at least one cranial nerve involved. In comparison of neck node status with cranial nerve palsy no difference in the incidence of palsy was found between N0 and N1-3. We consider this finding to confirm that a proportion of NPCs extend into the base of skull in the absence of lymphatic spread to the cervical lymph nodes.[19] Extension and invasion by the NPC into the cavernous sinus was found to produce lesions of nerves V, VI, and III, in decreasing order of frequency. The optic nerve was involved in the presence of parasellar invasion, and nerves X, XI, and XII were affected at the jugular foramen.

This study has confirmed that the majority of tumors arise laterally, usually from the fossa of Rosenmüller (82%) or the cushion of the eustachian tube. The degree of laterality found does not correspond with that of another study,[7] in which a lateral origin was found in only 44% of patients. It is possible that the very accurate visualization of the tumor obtained in our study by use of flexible nasoendoscopes may have contributed to a more precise localization of the tumor in the nasopharynx. The other techniques we routinely used, including use of rigid Hopkins rod telescopes to view the nasopharynx via both the mouth and the nose, were used if any difficulty in visualization arose. These instruments were used with the patient lying supine or sitting up with no local anesthetic. Biopsy of all nasopharyngeal lesions was thus conducted under direct vision with a Tilley-Heinkel forceps passed down the nasal cavity. A normal appearance to the nasopharynx was found in 6% of patients despite the presence of symptoms and Epstein-Barr virus serology strongly suggestive of NPC. In those cases the diagnosis was histologically confirmed by multiple deep biopsies of the nasopharynx under general anesthetic using a Yankauer's nasopharyngeal speculum and a Hopkins rod telescope, with computed axial tomography providing preoperative imaging of the tumor.

Symptomatic distant metastases were found in 5 of our patients, yet 19 had definitive evidence of distant metastases at the time of presentation. (Bone proved the commonest site, followed by lung and liver.) This finding confirms Neel's study,[16] in which 4% of patients had clinical evidence of distant metastases when first examined. All patients in our study with advanced locoregional disease were investigated with isotope bone or bone marrow scans, liver ultrasound scanning, and chest radiographs. Dickson[9] found that lung and liver metastases were more common than those in bone, but it is thought that variations in investigative practice may account for this finding, as other studies[20,21] as well as our own confirm bone to be the commonest site for distant metastases to develop. No patient in this study was found to have, or have had, any other Epstein-Barr virus–related tumor. Only 1 patient later developed a tumor in the head and neck region shortly after his NPC had been treated, and this was a squamous cell carcinoma of the larynx.

The stage of NPC at presentation is shown in Figs 4 and 5. Almost 80% of tumors in the nasopharynx are T2 or T3 when first presenting, and 75% of all patients have nodal disease, with 70% at stage III to V before treatment. At this institution[22] it is known that the 3-year relapse-free survival rate for stage I is 91%, stage II is 77%, stage III is 63%, and stage IV is 50% (1985 to 1987). Thus, if it were possible to educate the general population and physicians appropriately, especially in high-risk countries, it would be reasonable to expect patients to present earlier in the disease process, at stages I and II rather than III to V, and thus improve absolute survival. This educative process would have to be a national program, most likely conducted within schools and colleges for the general population. For the practicing clinician, encouragement to gain expertise in using the flexible nasoendoscope in the routine examination of all patients with any symptoms in the upper aerodigestive tract in high-risk countries may increase the number of patients presenting with less advanced NPC. We are sure that this is one approach to improving the overall prognosis for a neoplasm that affects a relatively young population. It may even be that mass screening of the population at risk with flexible nasoendoscopes, akin to gastroscopic screening of Japanese populations, could further improve the detection of small, minimally symptomatic NPCs.

ACKNOWLEDGMENT — We thank the secretarial and administrative staff of the Department of Clinical Oncology at Prince of Wales Hospital, Hong Kong, for their help in retrieving case notes.

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THE DEAFNESS RESEARCH FOUNDATION
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TINNITUS SUPPRESSION BY COCHLEAR IMPLANTS

WILLIAM S. MCKERROW, MD, FRCS
INVERNESS, SCOTLAND

CHRISTOPH E. SCHREINER, PHD, MD
SAN FRANCISCO, CALIFORNIA

RUSSELL L. SNYDER, PHD
SAN FRANCISCO, CALIFORNIA

MICHAEL M. MERZENICH, PHD
SAN FRANCISCO, CALIFORNIA

JOSEPH G. TONER, MD, FRCS
BELFAST, NORTHERN IRELAND

The beneficial effects of cochlear implants on tinnitus have been noted in several studies, but few detailed appraisals of the phenomenon have been made. Six patients fitted with the UCSF/Storz cochlear implant device were studied. The effects of use of the implant device on tinnitus were monitored, and suppression of tinnitus was tracked throughout periods of stimulation and poststimulation. Tinnitus was effectively suppressed in five of six patients with the device on and with noise input, and reduction of perceived tinnitus loudness occurred in four of six with the device on but without acoustic input to the speech processor. Unilateral stimulation frequently resulted in bilateral tinnitus suppression. These studies reveal that profound tinnitus suppression is obtained by patients using their cochlear implants. Further work is required to quantify the optimal mode of stimulation, but these findings suggest that tinnitus sufferers may ultimately benefit from development of electrical stimulation tinnitus suppression devices.

KEY WORDS — cochlear implant, tinnitus.

INTRODUCTION

The goal of effective tinnitus suppression for those patients whose lives are seriously affected by the symptom has so far been elusive. Since the advent of cochlear implantation, several investigators have noted the additional benefit of tinnitus suppression in some patients.[1-9] In several reports, a partial or complete abolition of tinnitus in implant patients has been described. However, the magnitude and time course of the suppression has not been well defined. It has been recognized that the phenomenon of tinnitus suppression by electrical stimulation has important implications for hearing tinnitus sufferers, and much work has been done exploring the possibilities for electrical long-term stimulation of the cochlea without impairing hearing. Strategies attempted have included transcutaneous stimulation,[10-12] tympanic membrane stimulation,[13] promontory and round window stimulation,[14-17] and intracochlear stimulation exclusively for tinnitus.[18] The results, although not without promise, have so far failed to indicate a reliable and innocuous method for tinnitus suppression.

The UCSF/Storz multichannel intracochlear device has been in use clinically since January 1985, with encouraging results for hearing.[19,20] Most patients have also reported improvement in their tinnitus while the implant is in use; some have reported residual inhibition and several have noticed suppression of contralateral as well as ipsilateral tinnitus. The mechanism of suppression of tinnitus in these patients remains unclear and the stimulus parameters that most effectively suppress the tinnitus are still poorly defined.

The effect of implant stimulation on tinnitus in a series of patients at UCSF is explored in this paper. The time course of changes in intensity, pitch, and annoyance levels was documented. Prior to testing, psychoacoustic parameters concerning the tinnitus were recorded for each patient as baseline information. Experimentally, the effect on the tinnitus when the device was switched on with no acoustic input was measured (inaudible 2- to 6-MHz carrier, hereinafter referred to as the control condition), along with the suppressive effects of the device in "normal" use, ie, with application of a continuous comfortable level of noise input. The reported findings encourage a further search for practical and effective stimulation strategies for use in hearing patients suffering from severe tinnitus.

PATIENTS AND METHODS

Six patients seen consecutively for routine evaluation of their hearing performance with their implants were included in this study. All had been fitted with the UCSF/Storz four-channel implant device.[19,20] In four patients, all four device channels were driv-

TABLE 1. BIOGRAPHIC DETAILS OF IMPLANT PATIENTS

Patient	*Sex*	*Age*	*Diagnosis*	*Implanted Ear*	*No. of Channels*
1	F	41	Ototoxicity	Right	4
2	F	63	Congenital syphilis	Right	3
3	M	63	Cogan's syndrome	Right	4
4	F	66	Unknown	Left	4
5	M	68	Familial deafness	Left	4
6	F	28	Cogan's syndrome	Left	2

From the Coleman and Epstein Laboratories, Department of Otolaryngology, University of California at San Francisco, San Francisco, California.

REPRINTS — Christoph E. Schreiner, PhD, MD, Coleman and Epstein Laboratories, Dept of Otolaryngology, University of California at San Francisco, San Francisco, CA 94143-0732.

en by their cochlear implant, in one patient three channels were driven, and in the sixth two channels were driven. All patients tested had a moderate, very good, or excellent result for hearing with the appropriate four-, three-, or two-channel speech processor.

All six patients responded to the questionnaire. None of the patients had had any previous treatment for tinnitus, and two patients had previous significant noise exposure during their hearing lives. The cause of the hearing loss in these patients was variable and is detailed in Table 1 with other biographic information. All patients had been fitted with the device at least 3 months prior to the study, and had tinnitus on the day of the study. Fully informed consent was obtained from each patient prior to the commencement of the study.

All patients were instructed to arrive on the day of the study without having used the device since the previous night, to reduce the possibility of long-range inhibition of tinnitus from previous usage. Their tinnitus was evaluated by the patient's subjective report referring to side, unilaterality or bilaterality, duration of the symptom, and the degree to which it interfered with the patient's life. A subjective description of the effect of the implant operation on the tinnitus was recorded, and the patient was also asked to describe the effect of device use on the tinnitus.

To quantify changes in the patients' tinnitus with stimulation, they were asked to scale the loudness, pitch, and annoyance of their tinnitus on a 10-point scale. A few practice examples were presented concerning tinnitus loudness to ensure the patient's complete understanding of what was required. Implant patients are well practiced in the use of magnitude estimation procedures, as these are used in their routine preoperative and postoperative evaluations.

Initial baseline estimations of these parameters were made by each patient at the beginning of the study, ie, without the patient's wearing the device. The device was then positioned on the head in the normal manner and switched on with the gain control on all four channels switched to zero so that only the carrier wave (2 to 6 MHz, depending on the channel) was delivered to the device, with no acoustic signal entering the external speech processor. Under this control condition all patients reported no audible sounds associated with the implant. Tinnitus loudness was estimated by the patient at 5-minute intervals thereafter. The data interval was reduced in duration if any rapid change in the tinnitus magnitude was detected. At each time mark, the patient was asked to independently scale loudness, pitch, and annoyance of the tinnitus by marking a position along an analog scale with 10 subdivisions. The extreme values at the end of each scale were identified, eg, as "not heard" and "extremely loud" for the loudness scale.

After a 30-minute period with the device on but without acoustic input, white noise was introduced at a comfortable level of intensity. The patient set this level at the external speech processor to match the normal mean level of operation of their device. The external noise level was approximately 50 dB (A-weighting filter). After a 30-minute period of noise stimulation with continued tinnitus estimates, the device was switched off and removed from the head. Responses were recorded until the tinnitus returned to the original level or appeared to stabilize.

An attempt was made to match the tinnitus with electrically evoked sensations in their quality, pitch, and intensity by use of the method of forced choice differential described by Vernon.[21] First, the quality of the tinnitus was assessed as either pure tone or narrowband noise. The loudness match was performed by stepwise increase of a tone or narrowband signal until the comparison signal evoked the same loudness as the tinnitus. For the pitch match, the patients had to choose from a number of signal pairs which of the two tones or narrowband center frequencies (neighboring audiometer settings between 125 Hz and 8 kHz) evoked a sensation that was more like their tinnitus.

Finally, in two patients the influence of isolated channels in suppression of the tinnitus was assessed by introducing the comfortably loud sound stimulus with each channel on in turn and asking the patient which channel or channels suppressed the tinnitus most effectively. The results of this evaluation were correlated with the pitch match of the tinnitus to assess the place specificity of electrical tinnitus suppression by the implant.

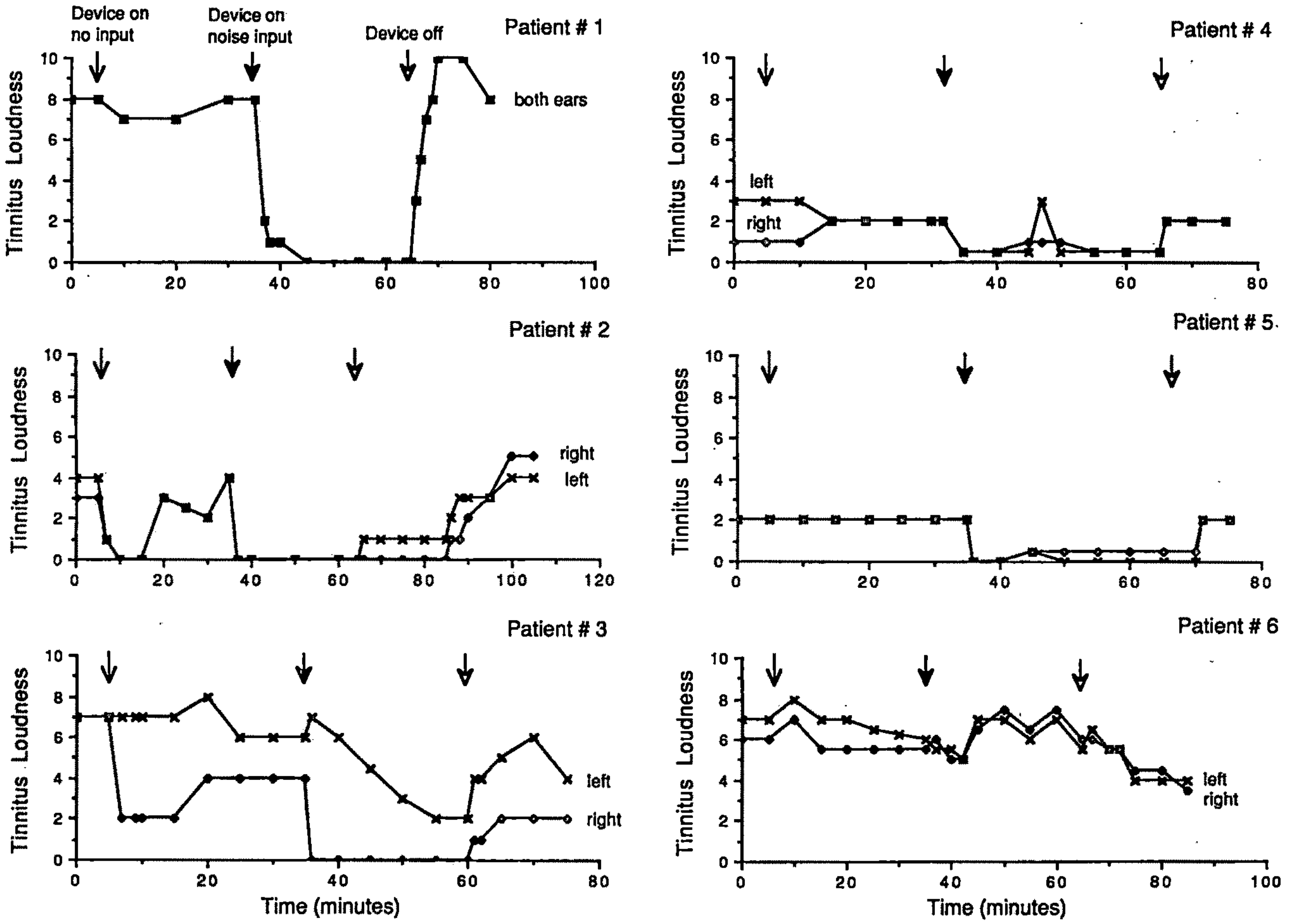
RESULTS

QUESTIONNAIRE RESPONSES

Patients responded to questions about their tinnitus under three separate conditions: 1) preimplant, 2) postoperative, implant off, and 3) implant on. The patients initially responded to questions on a scale of 1 to 10 and were then questioned by the investigator about the precise nature of the replies as a cross-check of accuracy of the patient's responses.

Side and Duration of Tinnitus. All the patients had had bilateral tinnitus for at least 1 year prior to the implant with the exception of one patient, who reported that he did not have tinnitus prior to operation. Four of the six patients had suffered from tinnitus for at least 5 years. In five of the six patients the tinnitus had remained constant following the implant operation, and in the sixth the tinnitus was now only rarely absent.

Types and Loudness of Tinnitus Sound. There were various types of tinnitus sound reported, from



Time course of tinnitus loudness before, during, and after use of cochlear implant device. Loudness was judged on arbitrary magnitude scale from 0 (undetectable) to 10 (very loud). Patients 1 to 3 were implanted on right side; patients 4 to 6 were implanted on left side. Arrows — changes in operation status of cochlear implant device, open arrowhead — device is switched on but receives no acoustic input (control condition), filled arrowhead — device is switched on and receives broadband noise of moderate level as input, unfilled arrowhead — device is switched off.

mixed tones like an organ to buzzing or ringing tones. A range of tinnitus pitches were also reported. Tinnitus pitch was altered by the use of the device in four of the six cases. One patient had great difficulty in understanding the concept of pitch, so alteration of pitch can only be reliably reported in five patients. All patients reported that they had more than one tinnitus sound after the implant operation with the device switched off, but all these sounds were altered or completely abolished when the device was in use. Of the four patients whose tinnitus was not completely abolished by the use of the device, one reported that his tinnitus loudness remained the same, although this report was not borne out by his subsequent testing. The other three patients experienced a substantial reduction in tinnitus loudness when the device was switched on.

Effect of Device Use. In response to a question concerning the effect of switching on the device, no patients reported worsening of their tinnitus. One reported no change on either side, and one reported a tinnitus reduction on the implanted side but no change in the contralateral ear. Two patients subjectively reported complete bilateral inhibition of the tinnitus, and one other said that he got complete abolition on the implanted ear with no change on the opposite side. The sixth patient experienced only moderate improvement in her tinnitus with device onset.

Effect of Device Offset. On switching off the device, four patients stated that the tinnitus essentially recovered immediately and one described its return within 15 minutes, suggesting a degree of residual inhibition. The patient who reported no change with the device on also reported no change on device offset.

EXPERIMENTAL RESULTS

Loudness Scaling. The decay of tinnitus loudness was plotted for each patient as a function of time (see Figure). The level of tinnitus charted on each plot is the subjective level attributed to the tinnitus by the patient on a scale of 0 to 10. The absolute scores for perceived loudnesses in different patients are not directly comparable, but the overall time courses of suppressive effects can be compared.

Patient 1 was unable to lateralize her tinnitus,

TABLE 2. TINNITUS MATCH

	Quality		*Pitch**		*Loudness (dB Sound Level)*	
Patient	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*
1	PT	PT	500 Hz	500 Hz	70	70
2	PT	PT	500 Hz	500 Hz	60	60
3	No data					
4	PT	NBN	8 kHz	1 kHz	80	50
5	PT	PT	1 kHz	1 kHz	45	45
6	NBN	PT	1.5 kHz	2 kHz	55	40

PT — pure tone, NBN — narrowband noise.

*500-Hz stimulus across implant evokes higher pitch, roughly matched to frequency location of channel 1 (22 to 23 mm from cochlear base). One kilohertz would match with channel 2; 1.5 and 2 kHz with channel 3; and 8 kHz with channel 4.

and her results are therefore plotted as a single line. For all other patients, separate curves represent scaled loudness of distinguishable ipsilateral and contralateral tinnitus components. Patient 1 experienced an initial mild suppression when the device was activated in the control condition, ie, without acoustic input, but the suppression waned after the first 10 to 15 minutes. Similar suppression during the control condition was noted in patient 2, in whom the effect was clearly bilateral, and also in patient 3, in whom the effect was on the implanted side only. Patient 4 had a similar although less marked ipsilateral effect, but she felt that her tinnitus in the unimplanted ear seemed to get slightly louder with the device on but without acoustic input. In patient 5 there was no evident suppression with the device in the control condition. Patient 6 reported a transient increase in tinnitus bilaterally over the first 5 minutes of the control condition, followed by a gradual bilateral decay in tinnitus after about the 10-minute time mark.

At the introduction of ambient noise at a comfortable level with the device switched on, ie, when the patients received a perceptible auditory stimulus for the first time, patients 1 through 5 noted a rapid reduction of tinnitus loudness to zero or near-zero levels — an effect that was maintained until device offset. The effect was bilateral in all but patient 3, who experienced a brief mild increase in tinnitus in the nonimplanted side, followed by marked decay of tinnitus magnitude on that side as well. Patient 6 experienced transient suppression of the tinnitus on the implanted side, but after 10 minutes of stimulation the tinnitus fluctuated just below or just above prestimulation levels. In her case, at device offset she began to notice a gradual decrease in the tinnitus on both sides that lasted for the duration of recording (20 minutes).

Device offset resulted in the other patients in a return of the tinnitus to prestimulation levels (or minimally above the starting level, in patients 1 and 2). The recovery was essentially immediate on device offset in patient 5. In patients 1 to 3 the return of the tinnitus was gradual; this finding suggested partial residual inhibition. In patient 2 residual inhibition was profound in the implanted ear and partial in the nonimplanted ear for about 10 minutes following device offset, and was followed by a gradual return to initial levels over the following 10 minutes.

The annoyance estimates of the tinnitus before, during, and after the use of the cochlear implant matched very closely the obtained loudness estimates and are therefore not discussed further.

Pitch Scaling. Patients 2 through 6 appeared to have a good understanding of the concept of pitch with reference to their tinnitus, but patient 1 tended to equate pitch with loudness and her results for pitch have been disregarded. Patients 4 and 6 detected no alteration of tinnitus pitch during the test apart from single transient (1- to 2-minute) episodes during which the pitch dropped and then returned to the previous level.

Patient 2, who had a marked suppression of loudness with the device on in the control condition, reported a simultaneous pitch fluctuation in both ears, the tinnitus being completely absent during noise stimulation and gradually returning to previous levels of pitch at device offset.

Patient 3 noted no marked change in pitch in the implanted ear with the device in the control condition. When the tinnitus reappeared after device offset, it fluctuated between the initial level of pitch and a much lower pitch level. In the contralateral ear, there were fluctuations of pitch throughout the period of stimulation, with a rapid return to near the previously scaled pitch values upon device offset.

Patient 5 reported no change in pitch with the device on but without acoustic input. He initially had complete tinnitus suppression with noise input, but when the tinnitus again became perceptible, the pitch was lower than it was previously; it returned to initial levels after device offset.

Tinnitus Matching. Each patient was asked to match the dominant tinnitus sound with reference to quality (wideband noise, narrowband noise, or pure tone), pitch, and loudness using the method of forced choice differential (see above). Although the results obtained could only be produced by asking the patient to compare the tinnitus with the electrically induced sensation of the sound presented by the device (rather than a true comparison with hearing), this was the only possible matching that could be applied in these profoundly deaf subjects. The results of this match are presented in Table 2.

It is probable that the peripheral or central source of the tinnitus varies with its frequency or its locations along the cochleotopic representational axis. Selective suppression of tinnitus by the implant channel most closely corresponding to the tinnitus source or representation should therefore occur. To test this hypothesis in patients 4 and 6, each channel of the device was activated in turn independently of the other channels. In patient 4, stimulation of channel 4 alone abolished the tinnitus; this finding also corresponded to the frequency match of her tinnitus at 8 kHz. Patient 6, who had relatively poor tinnitus suppression during the major part of the test and who was using a two-channel speech processor, did not feel that either of her two channels suppressed the tinnitus effectively.

DISCUSSION

Many authors discussing the results of cochlear implantation have observed that a varying proportion of their patients have noted tinnitus suppression while the implant is in use.[1-9] Thedinger et al[18] implanted a group of five patients using the House single-channel cochlear implant device solely for tinnitus with largely disappointing results — particularly with regard to hearing conservation. Nonetheless, there is little doubt that electrical stimulation of the cochlea does suppress tinnitus and can be used for this purpose in hearing patients.

All patients in the small group of deaf subjects fitted with the UCSF/Storz device seen consecutively during the period of the study experienced some alteration in their tinnitus sounds with the use of the implant, either in the quiet control condition or with sound input. In only one patient (patient 6) could the results be described as disappointing for tinnitus suppression, and her subjective impression was that her tinnitus was far less troublesome while the device was in use. In the other five patients there was marked reduction of tinnitus in the implanted ear with the device in use with noise, and in four of these, there was a reduction in tinnitus with the device on with no audible sound input. In two patients (patients 2 and 3) the control condition (device on without acoustic input) totally abolished tinnitus in the implanted ear, and in patient 2 this effect occurred bilaterally. This suppressive effect, however, tended to decay over this 30-minute control phase of the study in three of the four patients.

The recovery behavior of tinnitus after acoustic masking previously has been classified into five different patterns.[22] The recovery behavior after intracochlear electrical stimulation, as seen here, follows similar patterns. Five of the six patients fall into classes B and C of the previous classification, ie, show some poststimulatory reduction of tinnitus and subsequent recovery to previous values. One patient did not match any of the acoustic classes, but showed a slow poststimulatory decline of tinnitus magnitude.

It is interesting to notice that one of the two patients who were tested with isolated channels showed a channel-specific tinnitus reduction effect. The fact that the most effective suppressor channel also produced the best pitch match for the tinnitus indicates that the physiologic correlate of this particular tinnitus sensation was spatially restricted along the central or peripheral cochleotopic axis. Some frequency specificity of tinnitus suppression had been shown in earlier studies of electrical stimulation at the eardrum.[13] However, the frequency selectivity in that case may not have been related to the cochleotopic organization of the auditory system, since the stimulation site was constant.

Using the implant with a comfortable level of noise, five of the six patients experienced a bilateral suppression effect. In four of the five this effect was markedly bilateral — a fact verified by the reduction of annoyance levels to near zero in all four of these cases.

Placebo effects are difficult to eliminate completely from a study such as this, since double-blind studies are not feasible.[13] To this end, the point was made to the patients at the beginning of the study that the manipulations employed might make their tinnitus better, make it worse, or fail to alter it. Subjectively, five of the six patients had already noted prior to the study that their tinnitus was improved by the use of the implant.

MECHANISMS OF TINNITUS SUPPRESSION

The mechanism of tinnitus suppression by electrical means has not yet been clearly elucidated. In studies of masking conducted in 1971, Feldman[23] observed that a neural mechanism capable of blocking the spontaneous activity underlying tinnitus must be present that was effective in ipsilateral and contralateral ears. The effect appeared to be stimulus-dependent and more influenced by the intensity and duration of the stimulus than by its frequency. With direct electrical stimulation of the cochlea, the waveform and frequency of the stimulus appear to be of greater importance in achieving tinnitus suppression. In a study by Vernon and Fenwick,[11] asymmetric biphasic pulses were shown to be more effective than five other waveforms in the transcutaneous suppression of tinnitus.

Anodal DC stimulation has been known to be an effective suppressor of tinnitus for several years, but it is now well accepted to be damaging to neural structures and is thus unsuitable for tinnitus suppression in hearing patients. In the charge-balanced, capacitatively coupled UCSF device, DC leakage has been reduced to the minimum possible. Possibly remaining DC leaks were estimated to be below a few picoamperes. Whether the observed tinnitus suppression in the control condition (unmodulated carrier signal only, no auditory sensation) could be caused by such an extremely small DC current or whether other mechanisms related to the high-frequency carrier signal are responsible remains unclear.

Some workers have found the suppression effect to occur only ipsilaterally[14,16] and have postulated direct interference within the cochlea with the abnormal electrical signals that result in tinnitus. The unequivocal bilateral suppression seen in our patients challenges this simple model.

In patients with surviving hair cells, an electrophonic effect might be generated by electrical stimulation and act as a masker. However, the patients selected for implantation with the UCSF/Storz device are likely to have no surviving hair cells.[19,20] Direct electrical stimulation of afferent cochlear neurons, even at subaudible levels, will be relayed via the olivocochlear tract and cochlear efferent neurons to the cochleas of both ears, where alterations in cochlear micromechanics and biochemistry have been shown to occur.[24,25] It is conceivable that this effect could influence the strength of tinnitus. The observation of contralateral tinnitus suppression, however, indicates that the peripheral stimulation effect may result in centrally located interference effects, including the principal binaural nuclei.

IMPROVEMENT OF SUPPRESSIVE EFFECTS

Transcutaneous stimulation has been extensively evaluated[10,12] in tinnitus suppression, but the results are variable, perhaps because of the distance of the stimulus from the neurons. Promontory and round window stimulation appears rather more successful,[14-17] presumably because of the relative proximity to nerve endings that may be stimulated. With increasing distance, a proportionately greater stimulus is required for effectiveness, and this increase in turn may lead to unwanted electrophonic effects in addition to the unreliable tinnitus suppression.

From the results of this study, it is clear that strong suppression of tinnitus occurs with precise local application of stimulating currents to the region of the cochlear neurons, as achieved by the UCSF bipolar multichannel intracochlear implant. With intracochlear stimulation the stimulating current required can be minimized and conceivably kept below audible thresholds.

From this series it is evident that intracochlear electrical stimulation at current levels generating an audible response is more effective for suppressing tinnitus than is stimulation without auditory sensation. At the same time, it is important to emphasize that tinnitus *can* be strongly suppressed by nonaudible stimulation.[13] Further work with different stimulus waveforms and optimizing stimulus presentation sequencing will probably allow for stronger effective suppression without evoking sound sensations.

PRACTICAL IMPLICATIONS

Effective electrical tinnitus suppression may require the development of strategies for placing a stimulating electrode within the cochlea, possibly at the site corresponding tonotopically to the tinnitus frequency domain, and applying the minimal charge-balanced stimulus required to suppress the tinnitus.

Such a strategy would have to take account of the existing hearing of the patient and to minimize further compromise of that hearing. The presently employed round window route of electrode placement is unsuitable because of interference with basilar membrane mechanics. Direct placement of an electrode through the cochlear wall might allow precise stimulation of the required sector. The strategy must also take account of the need to prevent infection of the inner ear and leakage of perilymph.

There is real hope in the future that severely affected hearing tinnitus sufferers will benefit from electrical stimulation of the cochlea that does not significantly compromise hearing. Initial trials in already hearing-impaired individuals with severe bilateral tinnitus, the deafer ear being implanted, are justified when safe, less invasive implantation techniques are validated in animals.

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MODIFICATIONS OF THE NASAL CYCLE IN PATIENTS WITH HYPOTHALAMIC DISORDERS: KALLMANN'S SYNDROME

GIOVANBATTISTA GALIOTO, MD EMILIO MEVIO, MD PIETRO GALIOTO, MD
GABRIELE FORNASARI, MD MARIANGELA CISTERNINO, MD LORENZO FRAIETTA, MD
PAVIA, ITALY

The nasal cycle is a phenomenon characterized by cyclic changes in the airflow resistance of each nasal fossa from congestion or constriction of the nasal erectile tissue. This phenomenon is caused by alterations in the influence exerted by the autonomic nervous system and is believed to be regulated by a hypothalamic center. In order to verify this hypothesis on the hypothalamic regulation of the nasal cycle, the authors studied a group of subjects with Kallmann's syndrome. This disorder is characterized by coexisting hypothalamic hypogonadism and hyposmia or anosmia due to hypothalamic and olfactory center hypoplasia. An anomalous nasal cycle was found in all the subjects with Kallmann's syndrome. This disorder might be related to hypothalamus atrophy.

KEY WORDS — hypothalamus, Kallmann's syndrome, nasal cycle.

INTRODUCTION

The physiologic phenomenon marked by the periodic alternation of congestion and decongestion of the nasal erectile tissue in the two nasal fossae is known as the "nasal cycle."[1] In 1895 Kayser[2] described it for the first time and subsequent studies have confirmed its presence in 80% of normal subjects.[3-5] Like all the phenomena linked to the vasomotility of the nasal mucosa, this too is controlled by the autonomic nervous system, which alternates the action of its two components, ie, the sympathetic (vasoconstriction) and the parasympathetic (vasodilatation).[6]

However, in spite of the positive importance of the autonomic nervous system in this phenomenon, it is not yet fully clear how the alternation of the orthosympathetic and parasympathetic influences is actually regulated, and the regulatory center of such chronobiologic phenomena has not yet been clearly identified. Stoksed[7] and Eccles[8] located the regulatory center of this cyclic phenomenon in the hypothalamus. Their views are supported by the work of Malcomson,[9] who obtained nasal vasoconstriction in the cat following electrical stimulation of the hypothalamus.

In order to verify the hypothesis of Eccles on the regulation of the nasal cycle, it appears especially useful to study subjects with only hypothalamic lesions. We identified an ideal population in a group of subjects suffering from Kallmann's syndrome.[10] This disorder, also known as De Morsier's syndrome, is marked by the coexistence of hypogonadotropic hypogonadism and hyposmia or anosmia, and it is transmitted as an autosomal dominant trait. Its manifestations are related to a defective development of the rhinencephalon and of the hypothalamic site for gonadotropin-releasing hormone (GnRH) synthesis.[11-14]

In a previous study[15] on a small population of patients with Kallmann's syndrome, we had observed that the nasal cycle was absent in six of seven cases. We felt that such findings supported the hypothesis of a hypothalamic control of the nasal cycle. Several years later, we reviewed our previous results by repeating the study on a larger group of patients. In this latter study we were able to evaluate the effect of replacement hormonal therapy.

METHODS

Our aim was to check again the results obtained in our previous study[15] and to examine a larger number of patients, even though the cases are always rather few because of the rareness of the condition. We therefore reexamined the seven patients previously studied and added two new cases. Our population of Kallmann subjects thus included nine subjects from 10 to 26 years of age (Fig 1). The control population was a group of six patients with non-Kallmann hypogonadotropic hypogonadism (marked by the absence of a familial factor for hypogonadism and hyposmia, and by the hypophyseal site of the lesion). The ages of these patients ranged from 21 to 29 years. Most of the subjects (older ones) were receiving human chorionic gonadotropin (hCG) substitute hormone therapy and human follicle-stimulating hormone (Hu-FSH) extracted from urine (see Table).

Rhinoscopy was carried out in order to rule out morphologic anomalies or preexisting nasal or sinus diseases in the patients. The Smell Identification Test (SIT) (Sensonics Inc, Haddonfield, NJ) and Fortunato and Niccolini's[16] method were used for

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From the Departments of Otorhinolaryngology (G. Galioto, Mevio, P. Galioto, Fornasari) and Pediatrics (Cisternino, Fraietta), University of Pavia, Pavia, Italy.

REPRINTS — Giovanbattista Galioto, MD, Clinica Otorinolaringoiatrica, Policlinico San Matteo, ple Golgi 1, 27100 Pavia, Italy.

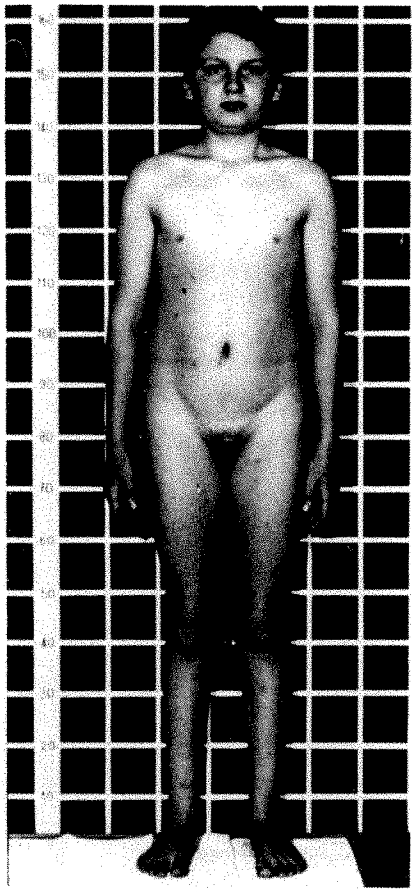

Fig 1. Subject affected by Kallmann's syndrome with characteristic hypogonadic development.

olfactory assessment in both nostrils.

On the basis of the SIT results the subjects were grouped as normal (35 ± 5 correct answers), anosmic (10 ± 5 correct answers), or hyposmic (between 20 and 30 correct answers), also defined as microsmia by Doty et al.[17] Fortunato and Niccolini's[16] method, using increment stimulation (10, 20, or 30 mL), was used to identify the detection threshold, as a confirmation of the olfactory threshold.

The nasal cycle was evaluated by active anterior rhinomanometry with a Mercury NR1 rhinomanometer. Data were analyzed with a suitable program set up for the purpose by our colleagues of the Department of Computer and System Sciences of the University of Pavia.

The nasal airflow was recorded for 6 hours at 20-minute intervals while the subjects remained in a room at constant temperature (24°C) and humidity (50%). Recordings were repeated in each subject for 3 days, always according to the same procedure. Pressure values were expressed in pascals and airflow was expressed as cubic centimeters per second. Mean values were subsequently plotted on a graph in order to reproduce the changes in the nasal cycle in each subject.

RESULTS

The nasal cycle was found to be anomalous in all subjects with Kallmann's syndrome. When we analyzed the morphologic characteristics of the tracings according to the classification of Hasegawa et al,[18,19] we found type 3 tracings in eight patients and a type 1 tracing in one patient (Fig 2[18,19]). Of the seven patients examined 4 years before, six showed unchanged morphologic features on the tracing with respect to the previous study. One patient, who had shown at the time a normal nasal cycle, was found to have an anomalous type 3 nasal cycle. In contrast, five of six patients with non-Kallmann hypogonadotropic hypogonadism showed a

CLINICAL CHARACTERISTICS AND TREATMENT OF KALLMANN'S PATIENTS AND CONTROL GROUP

					Treatment		
Patients	*Age (y)*	*Symptoms*	*SIT (%)*	*Familial Factor*	*hCG (IU/wk)*	*Hu-FSH (IU/wk)*	*Nasal Cycle*
Kallmann's syndrome							
1*	17	H + A	14	+	3,000 x 2	112.5 x 2	Anomalous
2*	10	H + A	13	+	—	—	Anomalous
3	21	H + A	7	+	2,000 x 2	75.0 x 2	Anomalous
4	23	H + A	10	+	3,000 x 2	75.0 x 2	Anomalous
5*	25	H + A	8	+	3,500 x 2	75.0 x 2	Anomalous
6	13	H + A	8	+	—	—	Anomalous
7	17	H + A	9	+	2,000 x 2	—	Anomalous
8*	25	H + H	24	+	3,500 x 2	75.0 x 2	Anomalous
9	22	H + H	25	+	3,000 x 2	150.0 x 2	Anomalous
Non-Kallmann hypogonadotropic hypogonadism							
10	21	H	37	–	2,000 x 2	75.0 x 2	Normal
11	29	H	35	–	500 x 2	225.0 x 2	Normal
12	24	H	35	–	3,000 x 2	75.0 x 2	Normal
13	22	H	38	–	3,000 x 2	75.0 x 2	Normal
14	16	H	37	–	2,000 x 2	—	Normal
15	18	H	36	–	2,000 x 2	—	Anomalous

SIT — Smell Identification Test, hCG — human chorionic gonadotropin, Hu-FSH — human follicle-stimulating hormone, H + A — hypogonadism and anosmia, H + H — hypogonadism and hyposmia, H — hypogonadism.

*Brothers.

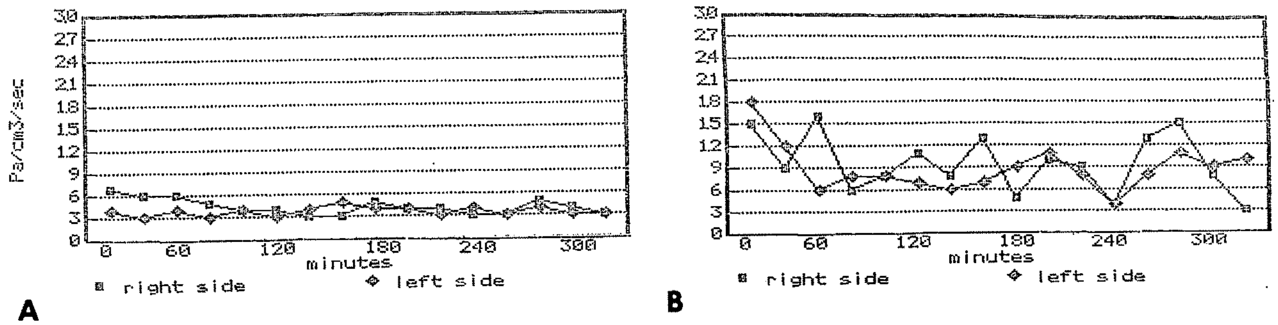

Fig 2. Nasal cycle patterns showing characteristics of classification of Hasegawa et al.[18,19] A) (Patient 1) Type 1 classification. B) (Patient 3) Type 3 classification.

normal nasal cycle (see Table).

Kallmann's patients had also olfactory disorders, ranging from hyposmia (two cases) to anosmia (seven cases). No such disorders were observed in the control population. In order to verify the relationship between olfactory damage and each group, we applied the χ^2 test with Yates' correction (2 x 2 table). We also applied Fisher's exact test. The results showed p values, respectively, of $< .001$ and $< .0001$.

DISCUSSION

Unlike other paired organs of the body, the nasal fossae show cyclic and reciprocal tone modifications of their autonomic innervation. According to the model proposed by Eccles et al,[20,21] the regulation of such alternation is controlled by a couple of "oscillators" located in the brain stem. The action of these oscillators is modulated by afferent data that reach them from the nasal mucosa and the respiratory center, and from a "body clock" located in the hypothalamus.

In the nasal fossa during vasoconstriction, and thus when the airflow is greater, the nerve endings are stimulated by thermal and hygrometric changes that result in the triggering of an inhibitory reflex leading to the modification of tone (decrease in the homolateral nasal fossa and increase in the contralateral one). Nasal vasomotor changes correlated to respiration (apnea or hyperventilation) are a response to the afferent data arriving from the respiratory centers.[20,22]

The presence in the hypothalamus of a high-level central generator for the nasal cycle has been demonstrated in animals in which electrical stimulation of the hypothalamus causes vasoconstriction of the nasal mucosa.[9] Eccles and Wilson[23] consider that vasomotor cycles are evident in the nasal fossae even when these are occupied by the probe of the plethysmograph, ie, even when the effect of temperature and humidity changes on the mucosa is cancelled. We can then conclude that the most important role in the regulation of such cyclic activity is played by the hypothalamic center.

Actually, we have been able to demonstrate that in Kallmann subjects, in whom hypothalamic atrophy is responsible for the disorder,[13,14,24] no nasal cycle can be detected. The lesion of the hypothalamic body clock, even when the function of the respiratory centers is normal, is thus sufficient by itself to modify the cyclic period of the autonomic phases at the level of the nasal mucosa. A normal nasal cycle is present in more than 80% of subjects with hypophyseal hypogonadotropic hypogonadism, a percentage that is comparable to that found in healthy subjects.[5] This fact should rule out the hypothesis of an altered luteinizing hormone or follicle-stimulating hormone release as the cause of cycle irregularities. This view is also substantiated by the absence of correlation between changes in the nasal cycle and variation in drug levels of the substitutive hCG and Hu-FSH or testosterone therapy.

Despite the olfactory deficits consistently found in our Kallmann subjects, the data we have obtained do not permit the identification of any interdependence between nasal cycle anomalies and olfactory deficits.

The case of the Kallmann subject with an initially normal but later, at the second testing, modified nasal cycle might be explained by a possible evolution of the hypothalamic damage with extension to the nasal cycle regulatory center.

ACKNOWLEDGMENT — We thank M. Curti of the Statistics Department for the statistical elaboration.

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EFFECTS OF PREOPERATIVE ELECTRICAL STIMULABILITY AND HISTORICAL FACTORS ON PERFORMANCE WITH MULTICHANNEL COCHLEAR IMPLANT

PAUL R. KILENY, PHD
JOHN L. KEMINK, MD
SUSAN ZIMMERMAN-PHILLIPS, MS
STEPHEN P. SCHMALTZ, MS
ANN ARBOR, MICHIGAN

We investigated the relationship between results of preoperative transtympanic electrical promontory stimulation, duration of deafness, postoperative implanted psychophysical results, and postoperative speech and speech sound recognition as indicated by a battery of five tests. Our subjects were 10 patients implanted with the Cochlear Corporation multielectrode implant, 1 year postimplantation, with a minimum of 17 active electrodes programmed in the bipolar + 1 mode. The results indicated that preoperative promontory thresholds, the slope of the threshold function, and the duration of auditory deprivation are excellent predictors of postoperative speech and speech sound recognition in the auditory (processor alone) mode. These results have significant implications for patient selection and counseling.

KEY WORDS — cochlear implant, deafness, electrical stimulation, psychophysics, speech recognition.

INTRODUCTION

The management of postlingual deafness by means of extracochlear or intracochlear electrical implants has gained nearly universal acceptance during the past 5 years. As indicated by the concerns discussed at the recent National Institutes of Health Consensus Development Conference on Cochlear Implants,[1] there are many unresolved issues regarding chronic electrical stimulation of the auditory system. Among those is the inability to accurately predict postoperative performance. A predictive ability might in the future lead to a prescriptive approach to cochlear implants that would be determined by both the pattern of the residual innervation and cognitive-linguistic abilities. It is thus important to evaluate the effects of preoperative factors on implanted performance. Some of these factors are relatively easy to quantify or define: for example, historical information, such as age at the onset of deafness, length of auditory deprivation prior to implantation, and physiologic measures, such as preoperative electrical thresholds and dynamic ranges. Others, such as the amount and distribution of residual stimulable neural (spiral ganglion) elements and degree of auditory dyspraxia (possibly related to the length of total auditory deprivation), are not readily available. The purpose of this paper is to investigate the relationship between preoperative factors and postoperative psychophysical factors and their effects on postoperative performance measures.

MATERIALS AND METHODS

There were two a priori criteria for inclusion in this study: patients had to have 1 year of postactivation experience with their Nucleus multichannel cochlear implant at the time of testing; and only patients with a minimum of 17 active channels activated in the bipolar + 1 mode were included. Table 1 lists the pertinent historical information on the 10 patients included in this study. At the time of testing for the purposes of this study, their ages ranged from 15 to 65. Age at the onset of complete auditory deprivation ranged from 3 to 57 years. The following preoperative measures were chosen: length of total auditory deprivation (DEP) (considered from the cessation of use of conventional amplification); length of effective hearing experience (EXP) (from birth to cessation of hearing aid use); and promontory electrical thresholds (PROM THR) and promontory dynamic ranges (PROM DR) of the ear that was subsequently implanted.

In order to account for the duration of auditory deprivation and the length of effective auditory experience by means of a single variable, we also calculated

TABLE 1. HISTORICAL INFORMATION

Subject	*Age (y)*	*DEP (y)*	*Average PROM THR (μA)*
1	15	4	18
2	35	6	8
3	33	7	12
4	65	8	19
5	65	11	23
6	42	16	15
7	54	50	33
8	58	55	60
9	42	35	17
10	37	20	15

DEP — length of total auditory deprivation, PROM THR — promontory electrical threshold.

From the Dept of Otolaryngology–Head and Neck Surgery (Kileny, Zimmerman-Phillips, Kemink) and the Clinical Research Center (Schmaltz), University of Michigan Medical Center, Ann Arbor, Michigan. Supported by National Institutes of Health grant P01 NS21440.

REPRINTS — Paul R. Kileny, PhD, Dept of Otolaryngology–Head and Neck Surgery, University of Michigan Medical Center, 1500 E Medical Center Dr, TC-1904, Ann Arbor, MI 48109-0312.

culated a ratio between length of auditory experience and duration of auditory deprivation. For instance, if a patient could no longer benefit from amplification at age 25 and was implanted at age 40, the value of the ratio, 25/15, was 1.6. In the case of a patient implanted at age 16 who ceased using a hearing aid at age 10, the value of the ratio, 10/6, will also be 1.6. This variable, which will be referred to as the auditory deprivation index (ADI), facilitates the comparison of patients of different ages. Promontory stimulation was carried out as follows. Biphasic rectangular charge-balanced square waves (50 Hz, 100 Hz, 200 Hz, and 400 Hz) were delivered in a 50% duty cycle mode (500 milliseconds on and 500 milliseconds off) via a Teflon-insulated tungsten needle electrode placed on the promontory transtympanically following local anesthesia of the tympanic membrane by means of iontophoresis or lidocaine hydrochloride injection. The tympanic membrane was visualized with an operating microscope, and if middle ear structures were identified (most commonly the lenticular process of the incus), the transtympanic needle was placed as far posteriorly as practical, approximately 2 mm below the visualized lenticular process. If middle ear structures were not identified, the needle was placed posteriorly in the upper middle third of the tympanic membrane. The needle was stabilized in position with cotton pellets in the external canal and a single piece of lightweight tape externally across the distal end of the needle. If no hearing sensation was elicited or if electrical stimulation resulted in pain sensation, the needle was repositioned slightly more posterosuperiorly. Contact with the promontory was determined by feel at placement and by monitoring the impedance of the electrode. Occasionally, contact needed to be reestablished by applying gentle pressure to the needle electrode. The return electrode was a surface electrode attached to the ipsilateral earlobe or mastoid process. Thresholds and dynamic ranges were determined by use of an adaptive procedure. The promontory data were processed as follows. For each patient, an average promontory threshold based on the four stimulus frequencies was obtained (PROM THR); similarly, an average promontory dynamic range was also calculated (PROM DR); the threshold and dynamic range of the 100-Hz square waves (100 Hz THR; 100 Hz DR) were also used individually in the data analysis because of the possibly exaggerated effect of stimuli with high thresholds on the average; finally, the slope of the threshold as a function of stimulus frequency was also calculated for each patient (SLOPE).

TABLE 2. VARIABLES INCLUDED IN DATA ANALYSIS

Variable	*Minimum*	*Maximum*	*Mean*	*SD*
DEP (y)	4	55	21.2	18.84
EXP (y)	3	57	23.4	19.34
ADI	.05	7.13	2.61	2.46
PROM THR (μA)	8	60	22	14.94
PROM DR (μA)	5	50	21.90	15.13
100 Hz THR (μA)	2.4	34	9.66	9.43
100 Hz DR (μA)	5.7	23	13.58	5.75
SLOPE	0.37	0.217	0.101	0.054
IMPL THR (μA)	127	540	312.9	114.22
IMPL DR (μA)	220	654	403.50	158.45
4-SPON (%)	8	95	71.20	29.16
VT (%)	20	70	49.20	17.49
SPON REC (%)	0	53	21.50	16.86
CID (%)	0	88	34.80	31.41
NU-6 (%)	0	43	13.40	16.60
AVE POST (%)	5.6	66.8	38.16	18.70

DEP — years auditory deprivation, EXP — years auditory experience, ADI — auditory deprivation index (DEP/EXP), PROM THR — average promontory threshold, PROM DR — average promontory dynamic range, 100 Hz THR — 100-Hz promontory threshold, 100 Hz DR — 100-Hz promontory dynamic range, SLOPE — slope of promontory threshold function, IMPL THR — average implanted threshold, IMPL DR — average implanted dynamic range, 4-SPON — Four-Choice Spondee Test, VT — Vowel Test, SPON REC — Spondee Recognition Test, CID — CID Everyday Sentence Test, NU-6 — NU-6 Test, AVE POST — averaged postoperative performance.

The postoperative psychophysical measures were the implanted thresholds (IMPL THR) and dynamic ranges (IMPL DR) averaged over all active electrodes. Charge-balanced biphasic rectangular pulses 200 to 400 microseconds in duration are delivered at a frequency of 300 Hz at a 50% duty cycle (500 milliseconds on and 500 milliseconds off) to each electrode, and thresholds and maximum comfortable levels are determined. For the purposes of this study, all implanted thresholds and dynamic ranges were determined by use of pulses with a duration of 205 microseconds for all patients.

Five subtests of the Minimal Auditory Capabilities Battery were used for evaluation.[2] The Vowel Test (VT) is a four-choice, 60-test item test consisting of vowels and diphthongs presented in a consonant-vowel-consonant context. The Four-Choice Spondee Test (4-SPON) consists of 20 items (spondee words) presented in a four-choice paradigm. The Spondee Recognition (SPON REC) test is an open-set test consisting of 25 spondee words. The patient's task is to repeat each stimulus word. The NU-6 Test (NU-6) consists of 50 monosyllabic words. Patients are required to correctly identify and repeat the stimulus words. The CID Everyday Sentence Test (CID) consists of 20 sentences including a total of 100 "key words." Patients are required to repeat the sentences. Scoring is based on correctly repeated key words.

DATA ANALYSIS

Because of the small number of subjects studied, the data analysis is mainly descriptive in nature. Spearman correlation coefficients are used as a robust measure of bivariate association: the first step in the data analysis was to generate a Spearman correlation coefficient matrix including all preoperative and postoperative variables. Data for individual variables are presented graphically by means of box plots or density stripes. A box plot is a graphic

TABLE 3. SPEARMAN CORRELATION MATRIX

	DEP	*EXP*	*ADI*	*PROM THR*	*PROM DR*	*100 Hz THR*	*100 Hz DR*	*SLOPE*	*IMPL THR*	*IMPL DR*	*4-SPON*	*VT*	*SPON REC*	*CID*	*NU-6*
DEP	1														
EXP	−.632*	1													
ADI	−.782†	.954§	1												
PROM THR	.559	−.393	−.340	1											
PROM DR	−.280	.657*	.541	−.037	1										
100 Hz THR	.322	−.230	−.136	.953§	.170	1									
100 Hz DR	−.133	.360	.283	−.393	.192	−.593	1								
SLOPE	.533	−.251	−.233	.887§	.133	.756†	−.119	1							
IMPL THR	.225	−.585	−.492	.250	−.540	.366	−.402	−.117	1						
IMPL DR	−.600*	.705†	.673†	−.474	.693†	−.525	.600†	−.117	−.815§	1					
4-SPON	−.522	.345	.399	−.289	.246	.052	.051	−.561	.172	.092	1				
VT	−.634*	.497	.566	.454	.093	−.190	.009	−.681*	.049	.117	.841§	1			
SPON REC	−.835§	.495	.591*	−.633*	.254	−.502	.276	−.661*	−.239	.530	.691†	.817§	1		
CID	−.657	.500	.450	−.835§	.348	−.627	.133	−.895§	−.076	.450	.542	.574	.685†	1	
NU-6	−.963§	.708†	.828§	−.505	.431	−.298	.184	−.494	.252	.656†	.429	.561	.772†	.671†	1

Shaded area is postimplant. For abbreviations, see Table 2.

*p≤.10.

†p≤.05.

§p≤.01.

method for displaying the 10th (bottom error bar), 25th (bottom of the box), 50th (line across box), 75th (top of the box), and 90th (top error bar) percentiles and values at the extremes of a variable, and is used to provide an indication of the shape of a distribution. Open circles represent data outside the 10th and 90th percentiles. A density stripe plot places vertical lines at the location of individual data values on a horizontal scale. Bivariate associations between data represented as density stripe plots are presented graphically with scatterplot matrices. The matrices describing the data are displayed without axis labeling, in order to facilitate the comparison of different bivariate relationships. Means, standard deviations, minima, and maxima of the variables included in the analysis are listed in Table 2 for reference purposes.

Since the main interest in this study was the definition of the relationship between the individual preoperative variables and postoperative performance, the five postoperative test measures (percent-correct scores for the Four-Choice Spondee Test, Vowel Recognition, NU-6, Spondee Recognition, and CID Everyday Sentences) were combined a priori into a composite measure of hearing performance by taking the simple average of the scores of the five tests. The relationship between this composite measure of performance and the preoperative variables was evaluated by means of Spearman correlation coefficients.

Finally, the subjects were divided into two groups ("prosthetic" and "assistive device") based on the following criterion performance scores on five postoperative speech recognition tests: Four-Choice Spondee (>50%), Vowel Test (>40%), Spondee Recognition (>20%), CID Everyday Sentences (>20%), and NU-6 (>10%). These criterion scores were chosen empirically on the basis of what the authors considered to represent prosthetic benefit from a cochlear implant, ie, the ability of open-set speech recognition in the auditory (processor alone) mode, without the benefit of speech-reading. Preoperative results as well as implanted thresholds and dynamic ranges were compared between the two resulting subgroups by means of Student's *t* tests.

RESULTS

Table 3 is a Spearman correlation coefficient matrix of all the variables included in this study. In general, auditory deprivation (DEP) correlates negatively with the postoperative performance variables, and has particularly high correlation coefficient values with the auditory deprivation index (ADI), Spondee Recognition (SPON REC), and CID Sentences (CID) and in particular with the NU-6 scores. The relationship between promontory threshold and its slope and the postoperative variables is similar, exhibiting particularly high correlation coefficient values with the results of CID Everyday Sentences. Of the two psychophysical postimplantation measures, implanted threshold (IMPL THR) and implanted dynamic range (IMPL DR), the only statistically significant correlation coefficient is between the implanted dynamic range and the NU-6 scores. The following general trends may be derived from the correlation matrix. Patients with high postimplant test performance scores have had longer periods of effective hearing than hearing deprivation, present with low average promontory thresholds and relatively flat threshold function, and once implanted, exhibit wider dynamic ranges.

Figure 1 illustrates the promontory thresholds of our subjects as a function of stimulus frequency by means of a box plot. As described by others for sinusoidal stimulation,[3,4] threshold increased with in-

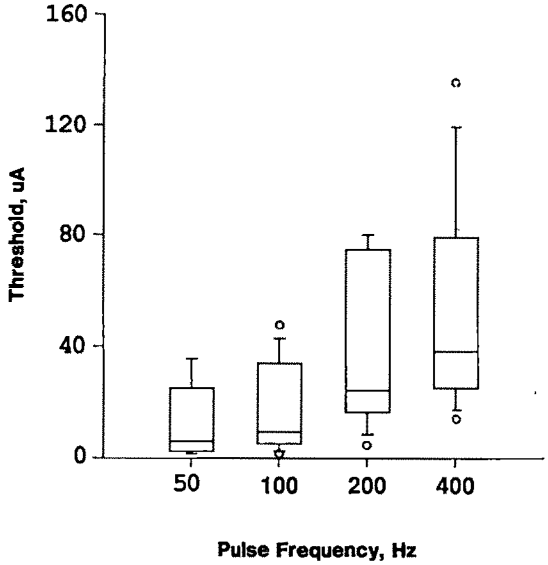

Fig 1. Promontory threshold ranges for 10 subjects as function of stimulus frequency. Thresholds increase with increased stimulus frequency.

creases in stimulus frequency for the square wave stimuli used in this study. There were few data points beyond the 10th to the 90th percentile range. This figure also illustrates a trend of increased threshold variability with increased frequency of stimulation. It is also apparent that patients with threshold values in the higher percentiles also had threshold functions with higher slopes.

Figure 2 illustrates the relationship between average promontory threshold (PROM THR) and scores (percent correct) of the five postoperative speech and speech sound recognition tests. For illustrative purposes, bivariate associations between the promontory threshold and test scores, illustrated as density stripe plots, are presented graphically by a scatterplot matrix. This representation allows the illustration of both the distribution of the individual variables and their relationship. As shown in the Spearman correlation coefficient table, the scatterplots indicate essentially that higher test scores are associated with lower promontory thresholds.

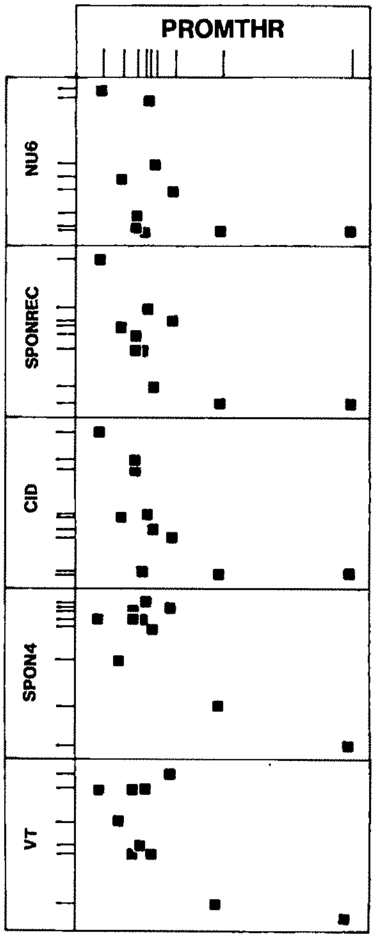

Fig 2. Matrix representing relationship between average promontory threshold (PROMTHR) and scores of five postoperative speech recognition tests. Variables are represented by stripe density plots; bivariate relationships are represented by scatterplots. SPONREC — Spondee Recognition Test, SPON4 — Four-Choice Spondee Test, VT — Vowel Test.

Table 4 lists Spearman correlation coefficients between preoperative historical information (DEP, EXP, ADI), promontory test results, and postimplantation psychophysical results, and the average composite postoperative speech recognition score, represented by the simple average of the five postoperative test scores. Particularly high coefficient values were obtained between hearing deprivation and the average postoperative score (−0.770, significant at the .05 level) and the slope of the promontory threshold function (−0.817, significant at the .01 level). The next-highest Spearman correlation coefficient was between the average promontory threshold and the average postoperative score (−0.638, significant at the .10 level). These relationships are illustrated graphically in Fig 3 by a scatterplot matrix between density stripe plots representing the average promontory threshold (PROM THR), promontory threshold slope (SLOPE), and the years of auditory deprivation (DEP) along the horizontal axis and the average postoperative speech recognition score (AVE POST) along the vertical axis. The most linear-appearing relationship was between DEP and the average postoperative score, which initially decreases quite rapidly as promontory threshold increases. The relationship between the promontory threshold slope and the average postoperative score appears somewhat nonlinear, in particular owing to the last data point. As indicated by the position of this subject along the density stripe plot for the slope, this particular subject was substantially separated from the distribution of the slope values for the rest of the subjects.

Figure 4 illustrates the relationship between implanted range and NU-6 scores. This Figure illustrates the abrupt transition in test scores beyond an average range of 300 μA (approximately equivalent to 125 programming units); this dynamic range marks the transition between presence and absence

TABLE 4. SPEARMAN CORRELATION COEFFICIENTS BETWEEN AVERAGED POSTOPERATIVE PERFORMANCE FACTOR AND PREOPERATIVE AND POSTOPERATIVE PSYCHOPHYSICAL MEASURES

	Correlation Coefficients
DEP	−.770*
EXP	.511
ADI	.552
PROM THR	−.638†
PROM DR	.298
100 Hz THR	−.373
100 Hz DR	.050
SLOPE	−.817§
IMPL THR	.043
IMPL DR	.345

For abbreviations, see Table 2.
*$p \leq .05$.
†$p \leq .10$.
§$p \leq .01$.

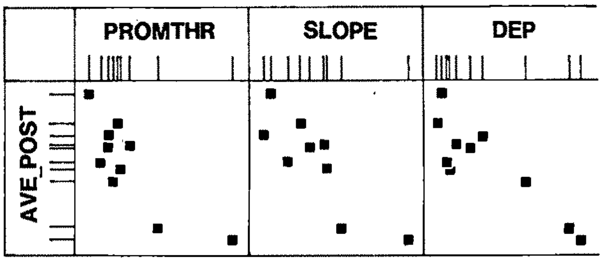

Fig 3. Matrix representing relationship between average postoperative score (AVE POST) and average promontory threshold (PROMTHR), promontory threshold slope (SLOPE), and auditory deprivation (DEP). Variables are represented by stripe density plots; bivariate relationships are represented by scatterplots.

of open-set speech recognition capabilities as indicated by the NU-6 test scores.

Finally, preoperative test results and implanted dynamic range and threshold values were compared by means of *t* tests between the two patient subgroups determined by the postoperative test results. On the basis of the predetermined criteria, 7 of the 10 patients were assigned to the better-performance (prosthetic) group and 3 to the lower-performance (assistive) group. Tests indicated significant differences between the two groups for years of auditory deprivation (DEP), experience (EXP), auditory deprivation index (ADI), promontory threshold (PROM THR), promontory dynamic range (PROM DR), promontory threshold slope (SLOPE), and implanted dynamic range (IMPL DR).

DISCUSSION

Patients attaining a substantial amount of open-set speech recognition in the auditory-only mode (without the benefit of speech-reading) may be considered to use the implant as a true prosthetic device. This type of performance with a cochlear implant is, as a rule, associated with patients who have lost their hearing postlingually, relatively recently prior to implantation. Other patients do not attain open-set speech recognition in the auditory-only mode, and their benefit from the cochlear implant may be characterized by the degree of enhancement of their speech-reading skills provided by the implant. These patients tend to be those who have lost their hearing at a relatively early age, many years prior to implantation. Clearly, these two categories of patients represent extremes defining various levels of benefit along a continuum. Since duration of auditory deprivation prior to implantation and the results of preoperative promontory stimulation are readily obtained, we studied the effects of these variables on postoperative performance.

Thresholds and Dynamic Ranges. To date there has been relatively little interest among cochlear implant teams in the United States in the clinical application and study of preoperative electrical stimulation in cochlear implant candidates. For instance, in a recent review paper,[5] promontory evaluation is mentioned briefly and is not considered to be a decisive factor in the determination of cochlear implant candidacy. Other papers dealing with large patient samples do not mention preoperative promontory stimulation at all.[6,7] There appears to be considerably more interest in preoperative electrical stimulation among our European colleagues. For instance, Meyer et al[8] and Hochmair et al[9] found promontory stimulation to be a valuable predictor of stimulability in their implanted patients. Recently, Brokx et al[10] investigated the relationship between residual preoperative hearing and electrical stimulation, and found significant correlations between preoperative audiometric thresholds and electrical dynamic range, temporal difference limen, and frequency discrimination.

As described by Shannon[11] for pulsatile stimulation and Pfingst et al[3] for intracochlear sinusoidal stimulation, promontory thresholds increased with increases in frequency (or a decrease in the phase duration of the rectangular biphasic pulses used in this study). At 100 Hz the thresholds obtained in our population ranged from a low of 2.4 μA to a high of 43 μA — a threshold range of 25 dB. These thresholds exceeded those obtained with sinusoidal intra-

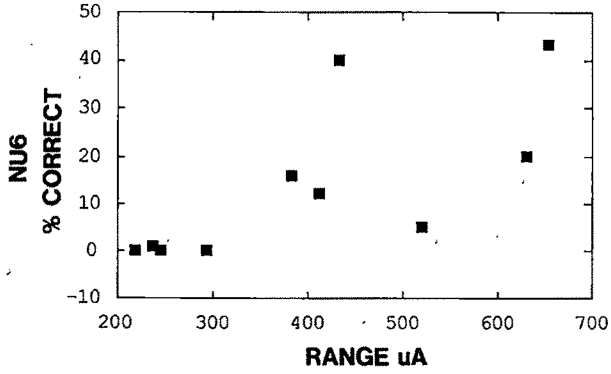

Fig 4. Scatterplot representing relationship between implanted dynamic range and NU-6 scores.

cochlear stimulation at 125 Hz reported by Pfingst et al in nonhuman primates, which ranged from a low of 0.1 μA to a high of 3.2 μA — a threshold range of 30 dB. These differences may be accounted for by differences in the mode of stimulation — promontory versus scala tympani — and by possible differences in spiral ganglion survival. Pfingst et al found that with some exceptions, low-frequency electrical thresholds correlated well with neural survival: low threshold coincided with good spiral ganglion survival within a 10-mm distance along Rosenthal's canal. In the present study, the average threshold correlated moderately well with the average postoperative speech sound recognition score (AVE POST). From the individual test results, it correlated best with SPON REC and CID scores. The average promontory dynamic range (PROM DR) emerged a poor predictor of postoperative performance. The reason for this may be the nature of the limiting factor determining the dynamic range: our observations indicate that especially for the higher-frequency, shorter-phase duration stimuli, the limiting factor tended to be pain that often preceded an uncomfortable loudness percept.

The promontory threshold slope emerged as an excellent preoperative predictor of the average postoperative performance. The slope reflects the difference between high-frequency thresholds (shown to correlate poorly with spiral ganglion survival) and low-frequency thresholds (shown to correlate well with spiral ganglion survival) and to some extent emphasizes the contribution of the low-frequency thresholds.

The average implanted threshold emerged as a surprisingly poor predictor of performance. This finding may be a function of the short-duration stimuli used to determine intracochlear implanted thresholds, 205 microseconds per phase. This short phase duration is in the range demonstrated to predict neural survival poorly.[4] On the other hand, implanted dynamic range, not limited by pain as in promontory stimulation but by loudness percept, emerged as a good predictor in particular of the NU-6 test scores.

Auditory Deprivation. The relationships between the various measures of auditory deprivation and the other variables followed predictable trends: short-term deprivation, long-term auditory experience, and a higher ADI value were associated with higher test scores and wider implanted dynamic ranges. In particular, these measures correlated well with the SPON REC and NU-6 test scores. The auditory deprivation index (ADI) or hearing experience/hearing deprivation ratio exhibited a particularly strong relationship with the NU-6 test results, only slightly less than did the auditory deprivation (DEP). The DEP was a close second to the SLOPE in its correlation with the average postoperative score.

CONCLUSIONS

For practical patient selection and counseling purposes, promontory thresholds, threshold slopes, and one of the measures of auditory deprivation appear to be the most useful. The only nonanatomic exclusion criterion in our practice is preoperative stimulability: a complete absence of preoperative stimulability is a contraindication for implantation in our program. Only 8% of the ears tested to date with promontory stimulation (60 patients implanted to date) did not stimulate preoperatively. One patient did not stimulate bilaterally with both transtympanic promontory and direct round window stimulation, and was not implanted. In the rest of the cases, the contralateral ear was stimulable. Ultimately, it is the patient who must make a choice whether or not to be implanted. The clinician must provide the patient with realistic predictions of postoperative performance. We believe that the combination of these simple preoperative measures provides us with the necessary information to fulfill this goal.

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ROLE OF QUINSY TONSILLECTOMY IN THE MANAGEMENT OF PERITONSILLAR ABSCESS

LCDR RICKY LOCKHART, MC, USN
PORTSMOUTH, VIRGINIA

CDR GREGG S. PARKER, MC, USN
PORTSMOUTH, VIRGINIA

THOMAS A. TAMI, MD
SAN FRANCISCO, CALIFORNIA

Peritonsillar abscess (PTA) is the most frequent complication of acute tonsillitis requiring surgical intervention. Debate continues concerning optimal therapy in terms of patient morbidity and cost-effectiveness. A retrospective study was performed on 45 tonsillectomies for PTA in military personnel from December 1986 through December 1988. Twenty-three quinsy (abscess) tonsillectomies and 22 interval tonsillectomies were identified. Parameters studied were age, sex, abscess location, interval prior to operation, blood loss, operative time, operative experience, and combined hospital and convalescent days for the two groups. Significant differences were noted between the quinsy and interval tonsillectomy groups concerning the average number of days hospitalized (3.0 versus 4.5) and their respective convalescent periods (10.3 versus 17.3). We conclude that quinsy tonsillectomy is the best management for PTA in a young work force when the optimal treatment choice is between interval or acute tonsillectomy.

KEY WORDS — peritonsillar abscess, tonsillectomy, tonsillitis.

INTRODUCTION

Peritonsillar abscess (PTA) is the most frequent complication of acute tonsillitis requiring surgical intervention. It is the most common deep infection of the head and neck and occurs most commonly in older children and young adults.[1-4] Inadequate treatment of PTA can result in complications varying from dehydration, jugular venous thrombosis, hemorrhage, and phlebitis to aspiration pneumonia, brain abscess, and airway obstruction.[5,6]

The appropriate management of this problem with respect to morbidity as well as cost-effectiveness continues to be widely debated. Recent studies that recommend aspiration alone or in combination with incision and drainage as the best and most cost-effective treatment[2,7-10] report a PTA recurrence rate of 0% to 22%. A long-term study of patients treated by incision and drainage with a 3½- to 8-year follow-up also quoted a recurrence rate for PTA of 22%. However, 49% had continued symptoms (22% PTA, 20% recurrent tonsillitis with fever, 7% episodic pharyngitis).[11] Most of these symptomatic patients were less than 40 years old (mean age, 26 years), a population encompassing most of the present military force. With emphasis on productivity and readiness, our policy has been to offer acute tonsillectomy as an alternative therapy for active duty members presenting with PTA. Since prior studies have suggested the efficacy and low morbidity of this technique,[4,5] we examined our experience treating active duty patients with PTA by either tonsillectomy or simple drainage. Factors potentially contributing to increased morbidity as well as the cost-effectiveness of these two treatment modalities in an active duty population were evaluated.

METHODS

A retrospective review of all active duty patients undergoing tonsillectomy for PTA from December 1986 through December 1988 was performed. Although 56 patients were identified, 11 cases were not included owing to incomplete follow-up or missing chart data. Of the remaining 45, 23 had undergone quinsy tonsillectomy, while 22 had interval tonsillectomies.

Data obtained on each patient included age, sex, abscess location, interval prior to operation, blood loss, operative time, and surgeon's level of experience. As an indicator of lost productivity, the total hospital and convalescent days for each patient were calculated. Operative findings and postoperative complications were also noted.

Our routine treatment protocol for patients with PTA consists of aspiration and/or incision and drainage followed by hospitalization. Intravenous fluids and antibiotics (usually penicillin G or clindamycin phosphate) are administered in addition to analgesic medications as needed. All patients in the quinsy tonsillectomy group underwent operation within 48 hours of admission (18 of 23 [78%] within 24 hours), while the interval group returned for operation during a second admission. Of these, 15 of 22 (68%) underwent operation within 2 months of their PTA and 20 of 22 (91%) within 3 months. Only 2 patients (9%) had their operations delayed for

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From the Department of Otolaryngology–Head and Neck Surgery, Naval Hospital, Portsmouth, Virginia (Lockhart, Parker), and the Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco, California (Tami). Sponsored by the Chief, Bureau of Medicine and Surgery, Washington, DC, Clinical Investigation Program (89-08-1969-65). The opinions or assertions expressed herein are those of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy or the Department of Defense.

REPRINTS — CDR Gregg S. Parker, MC, USN, Dept of Otolaryngology–Head and Neck Surgery, Naval Hospital, Portsmouth, VA 23708.

TABLE 1. AGE, SEX, AND SIDE OF PERITONSILLAR ABSCESS

	Quinsy (n = 23)	*Interval (n = 22)*
Age		
Mean	24.3	23.5
Range	18-39	19-34
Sex (M/F)	21/2	20/2
Location (R/L)	12/11	7/15

more than 3 months. All quinsy tonsillectomies and 16 of 22 interval tonsillectomies were performed under general anesthesia, while the remaining 6 interval tonsillectomies were performed under local anesthesia. All operations were performed by resident staff or rotating surgical interns under the guidance of attending otolaryngologists.

Statistical analysis of the data was performed by means of Student's pooled t test. Significance was defined as $p<.05$.

RESULTS

The age, sex, and sidedness of the PTA for the patients in this study are shown in Table 1. No statistical difference was noted between the two groups for any of these characteristics.

Eighteen patients in the quinsy group underwent operation within 24 hours of admission, and the remainder by 48 hours. Fifteen of 22 in the interval group underwent tonsillectomy within 8 weeks of their abscess. An additional 5 patients were operated on between 2 and 3 months after abscess drainage, and the remainder completed treatment by 8 months.

Intraoperative estimated blood loss and operative time for these two groups are illustrated in Table 2. No significant difference for either of these variables was noted. A significantly longer operative time was noted for the interval tonsillectomies done under general anesthesia compared to those done under local anesthesia.

The surgical experience of the operators is displayed in Table 3. While most of the tonsillectomies were done by residents at the postgraduate years 2 and 3 level, no significant difference in distribution was noted between the two groups.

The total hospitalization and convalescent time for these groups is shown in Table 4. The mean number of hospital days for the quinsy group was 3.0 with a convalescent period mean value of 10.3 days. The values for the interval group were 4.5 and 17.3 days, respectively. These differences were both significant ($p<.005$). The two separate hospital admissions in the interval group resulted in a much longer total hospital time and subsequent convalescent period.

TABLE 2. INTRAOPERATIVE BLOOD LOSS AND OPERATIVE TIME (MEAN±SD)

	Quinsy (n = 23)	*Interval (n = 22)*	*Interval (General) (n = 16)*
Blood loss (mL)	143±87	112±73	123±78
Operative time (min)	41±14	37±12	51±17*

*p<.005.

TABLE 3. SURGICAL EXPERIENCE OF OPERATORS

	Quinsy (n = 23)		*Interval (n = 22)*	
	No.	*%*	*No.*	*%*
Postgraduate year 1	2	9	1	5
Postgraduate year 2	10	43	11	50
Postgraduate year 3	8	35	8	35
Postgraduate year 4	3	13	1	5
Postgraduate year 5			1	5

Intraoperative findings in the quinsy group included bilateral abscess in 2 cases (9%), residual abscess in 3 cases (13%), and severe capsular fibrosis in 6 cases (26%). In the interval group, capsular fibrosis and scar was noted on the abscess side in 4 of 22 cases (18%).

There were no immediate or delayed bleeding complications in the quinsy group. In the interval group, two episodes of delayed bleeding occurred on postoperative days 2 and 8. Both were treated with local measures without further incident.

DISCUSSION

While optimal treatment of PTA remains controversial, consideration of total patient morbidity, lost productivity, and recurrence rates argues in favor of quinsy tonsillectomy as a reliable treatment. Studies in Europe by Moesgaard Nielsen and Greisen[12] and by Bonding[3] demonstrated a recurrence rate of 22% for peritonsillar abscesses treated by incision and drainage over a 4-year follow-up period. In the United States, Litman et al[13] also documented an average recurrence rate of 21% to 22% within 4 years of initial treatment. Bonding found that when followed up for up to 8 years, 20% of patients under 40 years of age continued to have recurrent tonsillitis and 7% had episodic pharyngitis.[3] In other words, 49% or roughly half of this population might be expected to experience substantial morbidity if treated conservatively without tonsillectomy. Since our military patient population mirrors that in these and other studies examining PTA,[4,14] these data provide strong support for seriously considering acute tonsillectomy as the initial management in these patients.

Operative morbidity was not higher for the quinsy tonsillectomy group. Comparison of the blood loss and operative times demonstrates that quinsy ton-

TABLE 4. HOSPITALIZATION AND CONVALESCENT TIME (MEAN±SD)

	Quinsy (n = 23)	*Interval (n = 22)*
Hospital days	3.0±.97	4.5±1.7*
Convalescent days	10.3±2.3	17.3±5.9*

*p<.005.

sillectomies have no significant increase in either of these variables. In fact, under general anesthesia, the interval group had considerably longer operative times. This finding probably reflects the presence of fibrosis of the tonsillar capsule, which has been well described in other studies following PTA[5,15] and was documented in 18% of our interval cases. The absence of complications in the quinsy group attests to the relative safety of this procedure. Two minor delayed hemorrhages occurred in the interval group and their significance, if any, would require a larger series of patients to evaluate.

The occurrence of bilateral abscess and/or residual pus in up to 21% of our quinsy patients also argues in favor of quinsy tonsillectomy, since some of these patients would not have been treated adequately with conservative therapy. This finding is well documented by other works in the literature.[4,14,16]

The most impressive difference between these two groups was in the total number of days of hospital and convalescent time required in their management. The total cost of operation and hospitalization for the quinsy group would be substantially less than that for the interval group, since only one hospitalization is required for these cases. Another, even more meaningful comparison, however, can be made by examining lost man-hours for the two groups. Including both hospitalization and convalescent days lost to the work force, the range for the quinsy group was 106 to 133 hours, while that for the interval group was 174 to 218 hours, based on an 8- to 10-hour average work day. Consideration of the total cost including the dollar value for lost man-hours as well as hospitalization further amplifies the cost-effectiveness of quinsy tonsillectomy.

Considering these various factors, what is the most efficacious, safest, and most cost-effective method of managing PTAs? Quinsy tonsillectomy certainly appears to meet these criteria for an active duty patient population. Outpatient methods described by Herzon and Aldridge[7] and others that require aspiration and/or incision and drainage of PTAs are often inappropriate for an active duty population. Furthermore, the natural history following an initial PTA treated conservatively will result in additional morbidity in up to 50% of patients in our population. In light of these factors, as well as military readiness considerations in this population, we feel that quinsy tonsillectomy is the treatment of choice for the acute management of PTA in an active duty population.

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EFFECTS ON COCHLEAR MORPHOLOGY OF REPEATED INSULTS TO THE STRIA VASCULARIS

ARNDT J. DUVALL III, MD
KAREN S. ROBINSON
MINNEAPOLIS, MINNESOTA

The interrelationship of stria vascularis and organ of Corti integrity was investigated. Strial morphology was altered by repeated injections of ethacrynic acid in the chinchilla. Although prolonged temporary strial damage was created, neither strial atrophy nor organ of Corti damage resulted.

KEY WORDS — chinchilla, ethacrynic acid, organ of Corti, stria vascularis, strial edema.

INTRODUCTION

The two most complicated cellular groups of the cochlear duct are the stria vascularis and the organ of Corti. It is reasonable to assume that the conversion of mechanical energy to chemoelectrical energy is greatly dependent upon their proper functioning.[1-3] How important is the integrity of one to the maintenance of the morphologic integrity of the other? In other words, is it possible to have damage to the stria vascularis function and/or structure and still maintain an intact organ of Corti? Conversely, is it possible to have a damaged organ of Corti without secondarily having damage to the stria vascularis?

Some insults result in damage to both, but in such a way that it is not possible to determine if it is the insult that directly damages both or if the damage to one results in damage in the other. Breaching the integrity of the cochlear duct results in organ of Corti degeneration and edema and atrophy of the stria vascularis.[4-8] However, we are unable to determine whether the loss of cochlear duct integrity with the resultant intermixing of endolymph and perilymph itself causes the damage to both simultaneously, or whether damage occurs first to one and then secondarily to the other. Severe acoustic trauma also causes both disruption of the organ of Corti and edema and atrophy of the stria vascularis.[9] However, it cannot be determined whether the acoustic trauma itself results in strial damage or whether the intermixing of endolymph and perilymph that inevitably occurs from the disruption of the organ of Corti is the cause of the strial damage. Venous obstruction of the cochlear outflow results in strial edema and atrophy as well as changes in the organ of Corti.[10] Again, we do not know whether damage to one causes damage to the other or whether the venous outflow obstruction itself causes damage to both primarily.

Aminoglycoside antibiotics cause severe atrophy of the organ of Corti, and yet most investigations have shown that the stria vascularis remains intact after systemic administration of such drugs.[11-15] Thus, an intact organ of Corti is not essential to the structural integrity of the stria vascularis. We do not know if the converse is true, ie, can we have damage to the stria vascularis and still maintain an intact organ of Corti?

Studies performed on several animal species have shown that a single dose of ethacrynic acid (EA) produces transient changes in strial morphology, ionic concentrations, and action potentials.[2,16-20] Strial edema occurs within 10 to 60 minutes, accompanied by a loss in endocochlear potential (EP).[1] With normal kidney function, a single injection of EA is presumed to be cleared from the body within 24 hours,[21] allowing strial structure and EP to return to normal within 24 hours.[18,22,23] There is some disagreement about the effect of EA administration on the organ of Corti, but most researchers have found that a low to moderate dose (10 to 30 mg/kg body weight) of EA does not cause temporary or permanent organ of Corti changes (A.J.D., personal observation, 1989).[19,24-26]

The present experiment was designed to determine if either prolonged or permanent damage to the stria vascularis, and thus an inferred loss of strial function, results in morphologic changes in the organ of Corti. Repeat dosages of 30 mg/kg EA at various time intervals were used to cause sustained damage to the stria vascularis.

MATERIALS AND METHODS

The EA solution was prepared by dissolving 240 mg of EA (Sigma Chemical Co) in 15 mL saline plus 1 mL 1N sodium hydroxide. The pH of the solution ranged from 11.5 to 12.5. The pH of the physiologic

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REPRINTS — Arndt J. Duvall III, MD, Dept of Otolaryngology, Box 396 UMHC, University of Minnesota, Minneapolis, MN 55455.

DOSAGE AND TIME REGIMENS

Group No.	*No. of Animals*	*Dosage*	*No. of Animals Killed at Each Time*				
			2 h	*6 h*	*24 h*	*48 h*	*1 wk*
1	10	EA, 30 mg/kg IV	3*	3*	4		
2	12	EA, 30 mg/kg IV					
		2 doses, 6-h interval			1†	1†	2
		3 doses, 6-h interval			1†	1†	6
3	15	EA, 30 mg/kg IV					
		10-14 doses, 24-h interval			6		
		24-h interval, rejected or not examined			9		
4	4	Saline IV					
		Single dose	2				
		14 doses, 24-h interval			2		
5	6	No injection					
6	3	EA, 30 mg/kg IV					
		Multiple doses, 2-h interval (varied anesthetics)			Not examined		

EA — ethacrynic acid, IV — intravenously.

*Strial thickness is significantly greater than normal.

†Strial thickness is significantly greater than that of * groups.

saline used in the control group was adjusted with 1N sodium hydroxide to match the pH of the EA solution.

Fifty chinchillas, obtained locally, were separated into six groups (see Table). Group 1 consisted of 10 animals that were given a single intravenous injection of 30 mg/kg EA and killed painlessly 2 hours (3 animals), 6 hours (3 animals), or 24 hours (4 animals) after the injection. Group 2 consisted of 12 animals given 30 mg/kg EA intravenously at 6-hour intervals for two or three injections. The animals were anesthetized with 0.2 mL ketamine hydrochloride intramuscularly prior to each EA injection. Two animals (1 that received two doses and 1 that received three doses) were killed painlessly 24 hours after the final injection; 2 similarly exposed animals were killed painlessly 48 hours after the final injection. The remaining 8 animals of this group were killed painlessly 1 week after the final injection. Group 3 consisted of 15 animals given multiple injections of 30 mg/kg EA intravenously at 24-hour intervals for up to 14 days and killed painlessly 24 hours after the last dose. The animals were anesthetized with 60 mg/kg sodium pentobarbital prior to EA injection. Group 4 consisted of 4 animals that were given an intravenous dose of pH-balanced saline in the same volume per kilogram body weight as the EA injections. Two animals given a single dose of saline were killed painlessly 2 hours after the injection. Two animals given multiple doses of saline 24 hours apart for 14 days were killed painlessly 24 hours after the last dose. As in group 2, the animals were anesthetized with 0.2 mL ketamine hydrochloride prior to each saline injection. Group 5 consisted of 6 uninjected animals that were killed painlessly; their cochleas were processed simultaneously with those of the other groups so as to serve as processing controls.

Group 6 consisted of three animals given 30 mg/kg EA intravenously at 2-hour intervals. The first two animals were anesthetized with sodium pentobarbital. The first animal received five doses of the drug totaling 150 mg/kg. The second animal received three doses of the drug totaling 87 mg/kg. The third animal was anesthetized with ketamine hydrochloride prior to injection and received three doses of the drug totaling 90 mg/kg. (See last paragraph of Results for explanation of varying of anesthetics.)

In preparation to being killed painlessly, the animals were injected intraperitoneally with 60 mg/kg of sodium pentobarbital. The animals were decapitated and the right bullae were removed. The round and oval windows were opened and a hole was made in the apex. Each cochlea was fixed by perfusing cold 2% osmium tetroxide through the round window within 3 minutes of killing. The cochlea was then immersed in 2% osmium tetroxide on a rotator for 2 hours, rinsed in 0.1 mol/L phosphate buffer (pH 7.4 to 7.5), dehydrated in a graded series of ethanols and propylene oxide, and embedded in Medcast. Scala media cross sections were cut from each turn of the cochlea at a thickness of 2 µm and stained with toluidine blue for light microscopic observation. The thickness of the stria vascularis was measured on scala media cross sections from all three turns by the method described in an earlier paper.[27] For electron microscopic observation, 20- to 30-nm thin sections were stained with lead citrate and uranyl acetate and viewed on a JEOL 100S transmission electron microscope.

The embedding method used for electron microscopy can cause artifactual changes in the position of Reissner's membrane. Therefore, the position of Reissner's membrane was not determined in this study.

RESULTS

Strial edema, the typical change seen in acute EA intoxication, was observed in the three animals killed 2 hours and in two of the three animals killed 6 hours after receiving a single dose (group 1; see Table and Fig 1A). Strial thickness was measured in normal animals, in those killed 2 and 6 hours after a single EA injection, and in those killed 24 to 48 hours after 6-hour repeated EA injections (Fig 2). Student's *t* test indicated that the strial thickness in the cochleas harvested 2 hours after injection was significantly greater ($p<.05$) than normal in all three cochlear turns. The strial thickness in the cochleas harvested 6 hours after injection was significantly greater than normal ($p<.01$) only in the second turn. A significant difference from normal was not observed in the first and third turns.

The strial edema was manifested by protrusion of

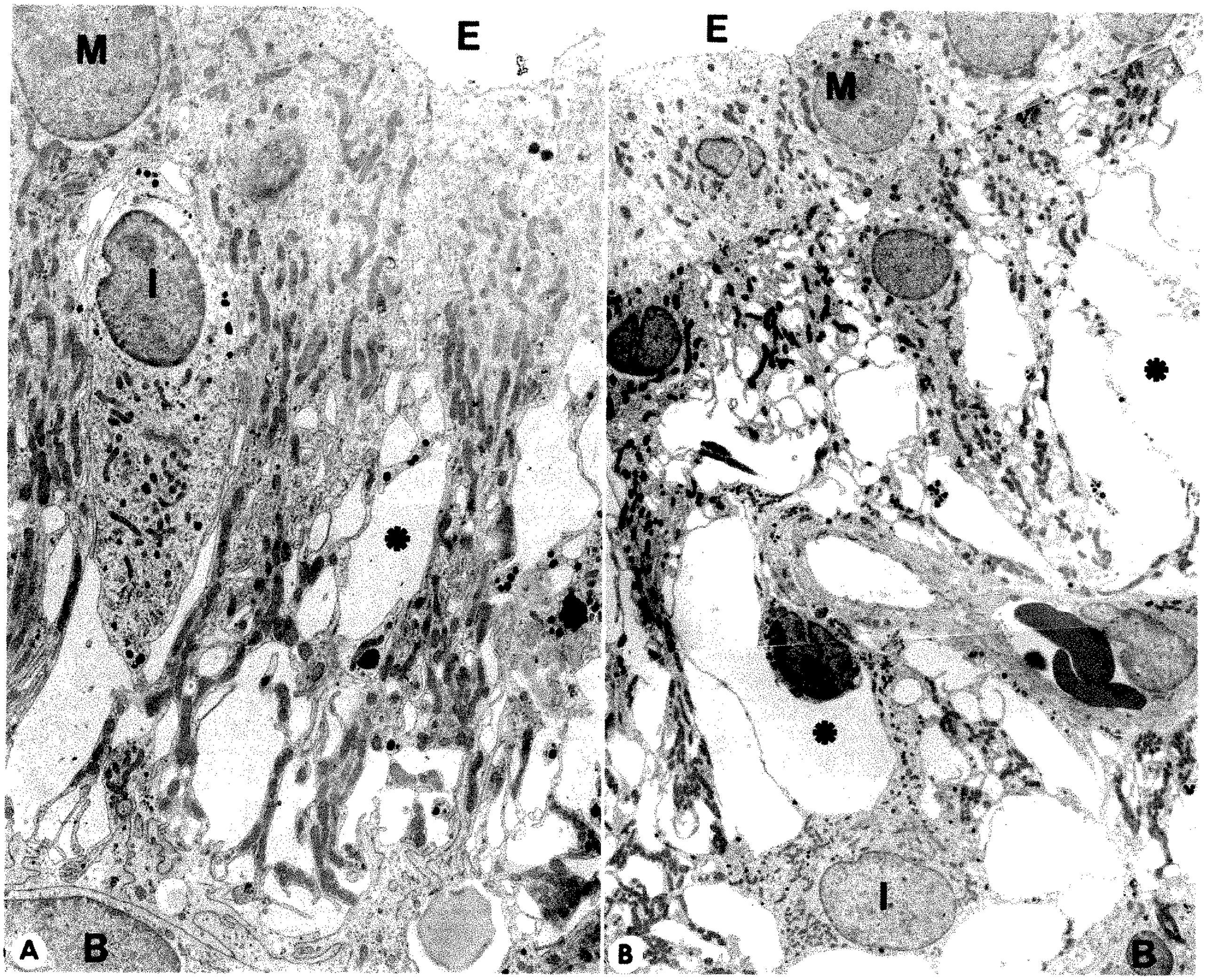

Fig 1. Electron micrographs of stria vascularis from first turn of right cochlea of chinchillas. Marginal cells (M) protrude into endolymphatic space (E), intermediate cells (I) appear shrunken, and there are large intercellular spaces (asterisks). Basal cells (B) appear normal. A) Chinchilla given intravenous injection of 30 mg/kg ethacrynic acid and killed 6 hours after injection (original x6,432). B) Chinchilla given three intravenous injections of ethacrynic acid 6 hours apart and killed 24 hours after final dose (original x3,500). Cellular extensions are somewhat retracted.

the marginal cells into the endolymphatic space, but the tight junctions at the endolymphatic surface were not disrupted, and the marginal cell processes maintained their usual orientation, which is toward the basal cells and in contact with the capillaries. The intermediate cells appeared shrunken, with mitochondria concentrated in the perinuclear region. The intercellular spaces were quite large, but despite the magnitude of the volume changes, the marginal and intermediate cell processes remained in contact with the pericapillary region and the basal cell layer. The basal cell layer, the spiral prominence, and the spiral ligament appeared unaffected. The organ of Corti and the stria vascularis appeared normal in all four animals killed 24 hours after a single intravenous dose of EA.

In the four animals killed either 1 or 2 days after multiple EA doses (group 2), massive strial edema was present (Fig 1B). The edema was much more severe than that seen in the striae vascularis of animals killed 2 and 6 hours after a single injection (Fig 1A), the strial thickness being almost three times that of normal (Fig 2). The strial thickness in the second and third cochlear turns of the 6-hour–interval animals was also significantly greater ($p > .05$) than the strial thickness observed 2 and 6 hours after a single injection. The organs of Corti from these four animals showed no morphologic alterations. The striae vascularis and organs of Corti of the eight animals that were killed 1 week after the final 6-hour–interval injection appeared normal at the light microscopic and electron microscopic levels.

Eight of the 15 animals in group 3, given repeat intravenous doses of EA at 24-hour intervals, died. One animal received 9 injections of the drug and, because of failing health, was killed 10½ hours after the last dose. This animal had strial edema, and the inner and outer hair cells of the first turn were severely degenerated. Since this animal was killed because of rapidly failing health, the damage seen

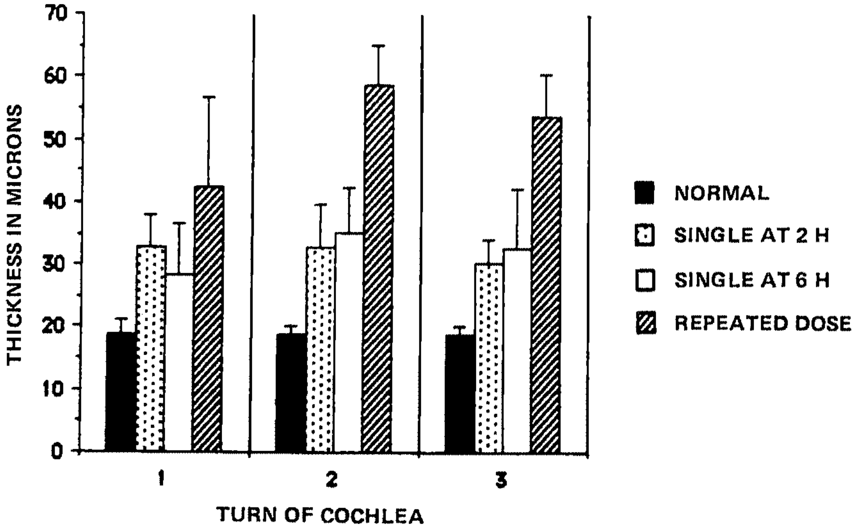

Fig 2. Comparison of changes in thickness (ordinate) by turn (abscissa) of stria vascularis following various dose regimens. Normal — no ethacrynic acid (EA), single at 2 h — 2 hours after single dose of EA, single at 6 h — 6 hours after single dose of EA, repeated dose — 1 or 2 days after repeated doses of EA 6 hours apart.

cannot be attributed solely to the effects of EA. The 6 remaining animals received 10 to 14 injections and were killed 24 hours after the last dose. Five animals had normal-appearing striae vascularis and all 6 animals had normal-appearing organs of Corti. Only 1 of 6 animals had strial edema present after 12 daily injections of EA. This animal had developed an iatrogenically thrombosed jugular vein on the 10th day of injection that may have reduced the blood outflow from the stria vascularis enough to cause edema. Kimura and Perlman[10] found strial edema within 1 hour of total obstruction of the venous outflow from the cochlea, and it proceeded to almost complete strial atrophy within 2 weeks.

The organ of Corti and stria vascularis of the two animals killed 2 hours after the saline injection and the two animals given daily intravenous saline injections for 14 days and killed 24 hours after the last dose (group 4) had appearances that were indistinguishable from those of the six cochleas from normal uninjected animals (group 5).

All three animals in group 6, given intravenous doses of EA at 2-hour intervals, died. The first animal, which received five doses of the drug, died within 16 hours of the last dose. The second animal was given three doses of the drug. This animal had trouble breathing and died within 18 hours of the last dose. Both animals had been anesthetized during each injection with sodium pentobarbital. To determine if the fatalities were due to the combination of EA and sodium pentobarbital, we changed anesthetics. The third animal was anesthetized with ketamine hydrochloride and given three doses of EA totaling 90 mg/kg. Although the animal seemed more alert than the two anesthetized with sodium pentobarbital, it still died 36 hours after the last dose. The fatalities seem to be due to the short intervals between EA injections. Postmortem examination showed that ileus had occurred. No cochlear morphology was performed in animals of this group.

DISCUSSION

Reported changes in organ of Corti function after EA injection include a decrease in summating potentials, the N1 portion of the action potential, and cochlear microphonics. It has been suggested that EA affects the function of the organ of Corti by altering membrane permeability and membrane impedance.[2,28-31] The present results imply that these changes do not progress to demonstrable changes in organ of Corti structure.

The changes in organ of Corti function are most likely caused by the reduction in EP after EA administration. An intact stria with its attendant normal EP is presumably essential for the proper function, if not the morphologic integrity, of the organ of Corti. Without the EP, the receptor currents through the outer hair cells would be impaired.[32,33] It is believed that the receptor current through the outer hair cells is intimately linked to the mechanical sensitivity of the cochlea near the characteristic frequency for any cochlear neuron, and that any reduction in receptor current, such as that caused by a reduction in EP, will result in a reduction in nerve sensitivity.

The strial edema seen 24 to 48 hours after repeated 6-hour insults is significantly greater than that following a single injection. This finding indicates that the effects of EA intoxication on strial integrity are prolonged and increased when the multiple doses are given at an interval that does not allow enough time between injections for the body to rid itself of the EA and/or for the stria vascularis morphology to return to normal. It is interesting to note that even though abnormal strial morphology and inferred loss of strial function persisted for at least 48 hours, the organ of Corti suffered no acute, histologically observable ill effect (1-week survival) from the inferred loss of EP.

It may be that prolonged alteration of organ of Corti function could eventually result in a change in organ of Corti morphology. If so, our study was apparently unable to cause malfunction for a sufficient time. Had the chinchillas been able to survive more than three doses of EA at 6-hour intervals, prolonged or permanent strial damage might have occurred and organ of Corti morphology might have been altered. The limiting factor in EA administration seems to be bowel toxicity resulting in ileus. Initially we injected EA intraperitoneally rather than intravenously, but abandoned this because the chinchillas died of ileus even when EA was given at 24-hour intervals. Ross[34] encountered the same problem in mice. Therefore, in order to study the effect of chronic alteration of strial function on the structure of the stria vascularis and organ of Corti, other methods must be sought.

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INTRACAVERNOUS CAROTID ARTERY ANEURYSM PRESENTING AS RECURRENT EPISTAXIS

JOHN GOLEAS, MD
MILTON L. PAIGE, MD
MICHAEL A. MIKHAEL, MD
ALLAN P. WOLFF, MD

CHICAGO, ILLINOIS

Massive epistaxis from a leaking intracavernous carotid artery aneurysm is a rare occurrence. Such an unusual case is presented with appropriate imaging and a successful treatment program.

KEY WORDS — aneurysm, epistaxis, intracavernous carotid artery.

A case of epistaxis is presented in which the diagnosis of an aneurysm of the intracavernous portion of the internal carotid artery (ICA) with erosion into the sphenoid sinus was made by magnetic resonance imaging (MRI) and confirmed by angiography and direct visualization at the time of operation. A brief discussion of the clinical presentation, the anatomy, the diagnosis, and the treatment of the lesion is made. The suggestion is put forth that MRI may be the diagnostic modality of choice and may alleviate the need for further tests.

CASE REPORT

A 66-year-old woman was seen in the emergency room on December 14, 1988, complaining of epistaxis. The bleeding had stopped at that time. Her past medical history was remarkable only for cluster headaches; she had no previous history of epistaxis, abnormal bleeding, hypertension, or trauma. Her workup was unremarkable and she was sent home, only to return later that day with brisk right-sided epistaxis. She was lightheaded, tachycardic, and hypotensive with a systolic blood pressure of 60 by Doppler. Laboratory testing revealed a 5-g drop in hemoglobin. Anterior and posterior nasal packs were placed, and she was resuscitated with intravenous fluids and 3 U of packed red blood cells. The epistaxis did not resolve with conservative measures but ceased after right internal maxillary artery ligation. After discharge she experienced occasional mild epistaxis and was readmitted in February 1989, when she presented again with brisk bleeding; hemostasis was obtained only after anterior and posterior ethmoid artery ligation. Even after these measures her epistaxis recurred, and she was readmitted in May 1989. An MRI study was performed (see Figure; A,B); a diagnosis of an intracavernous ICA aneurysm with extension into the sphenoid sinus was made. The findings were confirmed by angiography, which showed the aneurysm extending anteromedially from the carotid siphon (see Figure, C). Note that at no time did the patient exhibit cranial nerve abnormalities suggesting cavernous sinus syndrome.

Percutaneous detachable balloon occlusion of the intracavernous ICA was attempted but abandoned when the patient exhibited mental status changes during occlusion testing. She then underwent superficial temporal–middle cerebral artery bypass and Salibi clamp placement; during gradual occlusion of the ICA the patient developed a dense hemiparesis and hemineglect, necessitating removal of the clamp. Angiography revealed a patent bypass, a partially thrombosed aneurysm, and an embolus in the right posterior cerebral artery. As her hemiparesis resolved she was found to have a left homonymous hemianopsia, which slowly improved. The aneurysm was clipped at its base by direct frontotemporal craniotomy; a postoperative angiogram showed occlusion of the aneurysm at its base and no impingement on the lumen of the artery. Since the operation the patient's neurologic abnormalities have slowly resolved and she has had no further associated complaints.

DISCUSSION

Aneurysms of the ICA are rare and seldom considered as a cause of epistaxis in the otolaryngology–head and neck surgery literature. Most documented cases involve lesions of the intracavernous portion of the ICA eroding through the lateral wall of the sphenoid sinus, but aneurysms eroding directly into the ethmoid sinus[1] or rupturing into the petrous temporal bone[2,3] or directly into the eustachian tube[4] have been reported. Most cases have occurred after severe head trauma, but postoperative[5] and nontraumatic[6-11] aneurysms have also been documented. Pool and Potts[12] have estimated that these are due to trauma, arteriosclerosis, and congenital malformations 70%, 25%, and 5% of the time, respectively. The mortality from traumatic aneurysms is estimated to be 30% to 50% by various researchers; usually diagnosis is made within 3 weeks of the traumatic event, when the patient presents

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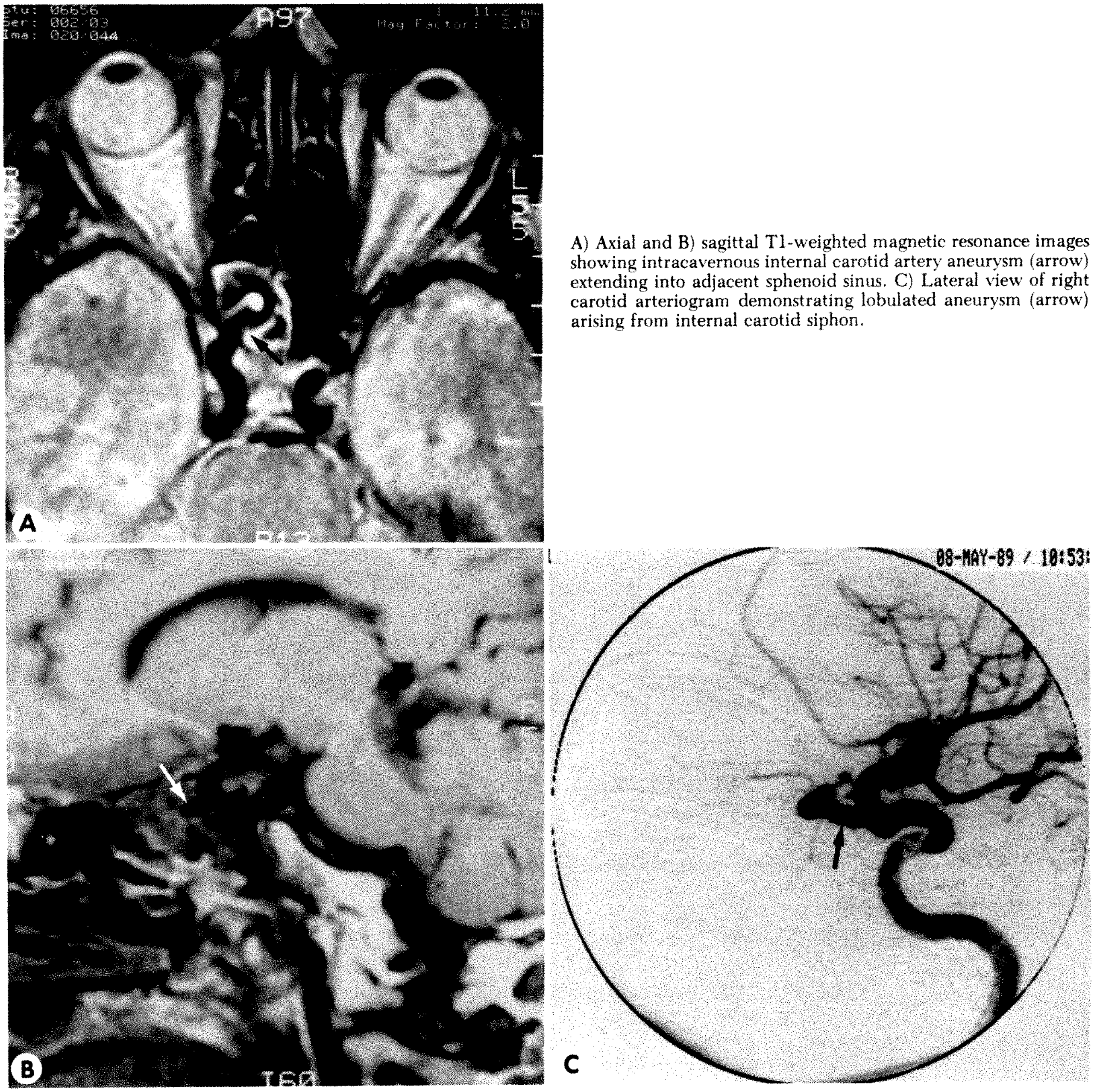
From the Divisions of Otolaryngology–Head and Neck Surgery (Goleas, Wolff) and Neuroradiology (Mikhael, Paige), Evanston Hospital and Northwestern University, Chicago, Illinois.



A) Axial and B) sagittal T1-weighted magnetic resonance images showing intracavernous internal carotid artery aneurysm (arrow) extending into adjacent sphenoid sinus. C) Lateral view of right carotid arteriogram demonstrating lobulated aneurysm (arrow) arising from internal carotid siphon.

with massive epistaxis, although cases have been reported in which delays of up to 40 years have elapsed before the initial episode of epistaxis occurred.[13] Presumably trauma can cause either a traumatic aneurysm or rupture of a previously existing congenital aneurysm, and it is often associated with Maurer's triad, which consists of unilateral blindness, an orbital rim fracture, and massive epistaxis.[14]

The close proximity of the intracavernous portion of the ICA to the sphenoid sinus is well known. Renn and Rhoton[15] noted the carotid artery bulging into the sinus in 71% of their specimens; it was usually covered by a thin layer of bone, but 4% of the specimens had no bony layer and were covered only by dura and sinus mucosa. They also found that in 66% of their specimens the bony layer was less than 1 mm thick.[15] Because of the intimate anatomic relationship of the intracavernous portion of the ICA to other cavernous sinus structures, aneurysms here are often associated with injury of the optic nerve and the ophthalmic artery, the oculomotor, trochlear, and abducens nerves, and/or the trigeminal nerve (primarily the first and second divisions); the olfactory nerve may also receive damage, resulting in findings that may include anosmia, blindness, facial numbness, and/or oculomotor palsy.[1,8,9,16] Associated hemiparesis,[17] aphasia,[8] Horner's syndrome,[2,9] and diabetes insipidus[18] have also been reported, but are unusual.

Early diagnosis of a carotid aneurysm is essential if death from exsanguination is to be prevented. Although seldom considered in the differential diagnosis of epistaxis, the possibility of an aneurysm increases greatly with a previous history of head trauma, particularly when the bleeding is massive. Any evidence of cavernous sinus syndrome also supports the diagnosis. In recent years computed tomography has been used to detect fractures and examine the paranasal sinus anatomy; unilateral opacification of the sphenoid sinus, occasionally with an enhancing rounded mass, may be seen. Cerebral arteriography is considered to be the procedure of choice for definitive diagnosis of the aneurysm. In the case presented we were led to the diagnosis by the patient's resistance to standard surgical therapy. The MRI images were diagnostic of the abnormality and suggest the usefulness of this technique in future cases.

Various authors have reported the successful use of intranasal balloon catheters as a temporizing measure when epistaxis occurs from an ICA aneurysm.[19,20] Once it is diagnosed, most would consider immediate surgical intervention to be mandatory, as conservative therapy has been shown to carry a 40% to 50% mortality rate. Accepted treatments include internal or common carotid artery ligation, a trapping procedure, or eradication of the aneurysm itself by electrothrombotic coagulation, detachable intravascular balloon occlusion, or direct surgical clipping.[1-3,5-9,16,21]

SUMMARY

An aneurysm of the ICA should be considered in any search for the cause of epistaxis, particularly when the bleeding is massive, associated with head trauma, or not responsive to standard therapies. An opacified sphenoid sinus and evidence of bony destruction by computed tomography is suggestive of the entity and makes angiography mandatory. Our experience has shown that MRI can provide the diagnosis with certainty; perhaps this paper will initiate its early use when the presence of an intracavernous carotid artery aneurysm is suspected clinically.

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ABOLITION OF OPTOKINETIC AFTERNYSTAGMUS BY AMINOGLYCOSIDE OTOTOXICITY

TIMOTHY C. HAIN, MD
CHICAGO, ILLINOIS

DAVID S. ZEE, MD
BALTIMORE, MARYLAND

We studied optokinetic afternystagmus in eight subjects with loss of or impairment of vestibular function due to ototoxic antibiotics. We found that the initial amplitude, the time constant, and the slow-phase cumulative eye position of optokinetic afternystagmus were significantly reduced in the patients. Slow-phase cumulative eye position most reliably distinguished our patients' responses from those of a normal group.

KEY WORDS — optokinetic afternystagmus, ototoxicity, vestibular function.

INTRODUCTION

In normal human beings, movement of the entire visual environment induces a compensatory rotation of the eyes called optokinetic nystagmus (OKN). Although evaluated routinely in patients with vestibular diseases, OKN is insensitive to vestibular lesions except in acute unilateral vestibular lesions accompanied by spontaneous nystagmus.[1]

Zee et al,[2] observing reduction of optokinetic afternystagmus (OKAN) in three human subjects who had decreased vestibular function due to meningitis, suggested that abnormalities of OKAN might be a more sensitive indicator of a vestibular lesion than OKN. Optokinetic afternystagmus is the nystagmus that follows OKN after the lights are extinguished. It is thought to reflect the component of the optokinetic response due to activation of the vestibular nucleus.[3] Bilateral labyrinthectomy completely abolishes OKAN in animals.[4-6]

The effects of ototoxicity on OKAN have previously been reported in a total of six patients.[7,8] Here we report the effect on OKAN in eight additional patients with bilateral decrease of vestibular function due to exposure to ototoxic antibiotics.

SUBJECTS AND METHODS

The Table gives demographic data for our subjects. All patients complained of oscillopsia, and all had diminished vestibular responses to chair rotation. The mean vestibulo-ocular gain in response to an impulse of acceleration resulting in a constant velocity rotation at 60°/s was 0.15±0.06 (lower limit of normal is 0.4). The mean vestibulo-ocular time constant was 4.2±1.4 seconds (lower limit of normal is 10 seconds).

Horizontal eye movements were recorded by DC electro-oculography with miniature silver–silver chloride electrodes. Vertical eye movements and blinks were registered by electrodes placed above and below the right eye. Eye position signals were amplified differentially (Tektronix 5A22 amplifier), low-pass filtered (3-dB point, 40 Hz), and then sampled at 100 Hz with 12-bit resolution by a laboratory computer.

The subjects were seated inside a 1.2-m (4 ft)–diameter optokinetic drum. The inside of the drum had black squares placed randomly on a white background and extended 1 m above and below the line of sight.[9] The subject's head was stabilized by a chin rest. Optokinetic nystagmus was induced by rotating the drum at 60°/s.

Figure 1A shows the stimulus profile. In each trial optokinetic stimulation lasted for 87 seconds. The subjects were instructed to "Look at the squares as they pass directly in front of you." During each trial the lights were switched off for 2 seconds at 12, 26, 40, and 60 seconds after the onset of optokinetic stimulation to "sample" the OKAN.[10] At 87 seconds after the onset of stimulation, the lights were switched off for 1 minute to record the decay of OKAN. The first 30 seconds of this longer dark period was collected in order to calculate the time course of decay of OKAN. After 60 seconds of darkness the lights were switched back on in order to maintain a constant corneoretinal potential. The

COMPOSITION OF PATIENT GROUP

Patient	*Age (y)*	*Sex*	*Agent*	*Duration (d)*	*Indication*
1	55	M	Gentamicin	30	Sepsis
2	57	M	Gentamicin	37	Sepsis
3	79	M	Streptomycin	90	Meningitis
4	63	F	Gentamicin	14	Peritoneal dialysis
5	43	M	Gentamicin	30	Sepsis
6	48	M	Streptomycin	50	Tuberculosis
7	68	M	Gentamicin	30	Peritoneal dialysis
8	79	F	Gentamicin	30	Sepsis

From the Departments of Neurology (both authors), Ophthalmology (Zee), Otolaryngology (both authors), and Neuroscience (Zee), The Johns Hopkins University School of Medicine, Baltimore, Maryland. This research was supported by research grants EY00914 (T.C.H.), EY001849 (D.S.Z.), and EY01765 (Core Grant) from the National Institutes of Health/US Public Health Service.

REPRINTS — Timothy C. Hain, MD, Dept of Neurology, Northwestern Memorial Hospital, Superior and Fairbanks, Passavent 10, Chicago, IL 60611.

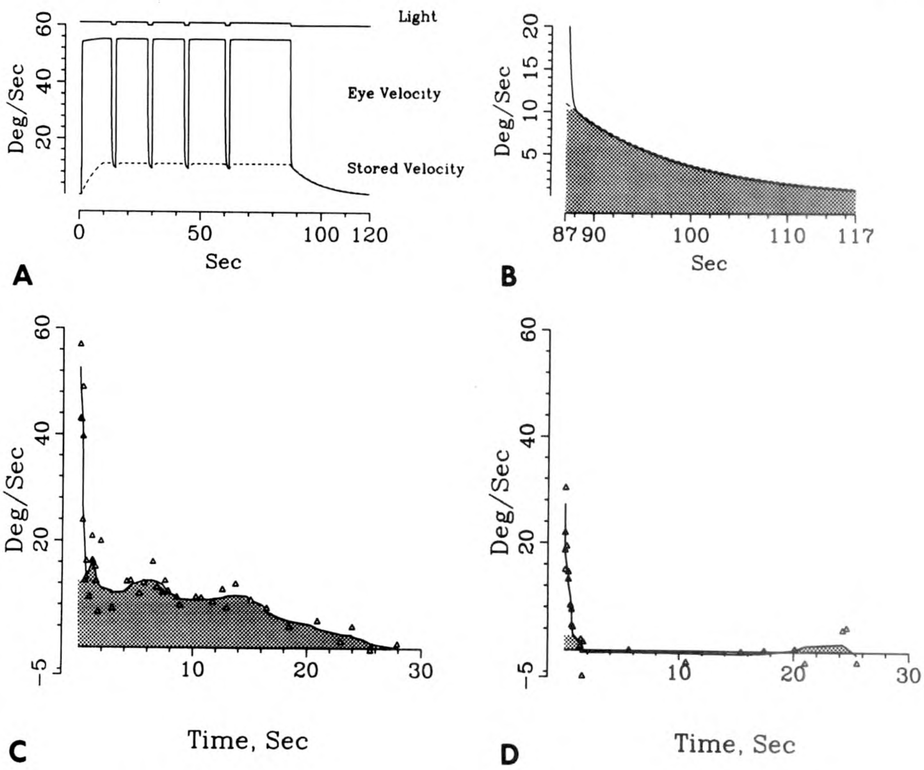

Fig 1. Method of quantifying optokinetic afternystagmus (OKAN). A) Stimulus profile. B) Portion of OKAN used to calculate slow-phase cumulative eye position. C) Velocity trace for OKAN in normal subject. D) Velocity trace for OKAN in patient.

arrangement of samples allowed us to obtain five values for OKAN initial velocity during each trial of optokinetic stimulation. Subjects were encouraged at the beginning of each trial, but otherwise no other alerting maneuvers were used. During the periods of darkness the subjects were told to "Look straight ahead." Eye position was calibrated at the beginning of each pair of trials by having the patient alternately view one of two light-emitting diodes located 40° apart.

Slow-phase velocity of nystagmus was calculated with a manually assisted computer program. Figure 1B-D shows eye velocity traces. Figure 1B,C shows normal OKAN responses — 1B being idealized, and 1C an actual response taken from a normal subject. Figure 1D shows an actual response from a patient with ototoxin exposure. Initial velocity was based on mean slow-phase eye velocity during the 1.0- to 2.0-second period after the lights were extinguished. This calculation was made during four 2-second samples and at the start of the 1-minute period of darkness. Slow-phase cumulative eye position (SCEP) was calculated by numerically integrating the area under the first 30 seconds of the slow-phase velocity curve, excluding the first 2 seconds, and considering eye velocity directed contrary to drum rotation as zero. To this quantity was added the mean initial velocity calculated from the samples, multiplied by 2.0 (which was the period over which the samples were obtained). The time constant of decay of OKAN was calculated by dividing the SCEP by the initial velocity and adjusting the results with a correction factor. Normal comparison data were obtained from 30 normal subjects as reported previously.[11]

RESULTS

Figure 2A shows the distribution of the values of OKAN initial velocity among the eight patients compared to the distribution in normal subjects. The values for our patients were calculated from 10 samples per subject, combining leftward and rightward values. The average initial velocity in the patients was 6.0°/s ± 2.7°/s (mean ± SD) as compared to 10.9°/s ± 2.9°/s found in normal subjects. The range of means for initial velocity was 2.5°/s to 11.8°/s. Although the mean initial velocity in patients is significantly different from that of the normal subjects ($p < .0015$, Mann-Whitney U test), there was overlap between the lower fifth percentile limit of normal (5°/s) and the individual values exhibited by our patients.

Figure 2B shows the distribution of the mean individual time constants calculated from two trials. The overall mean time constant was 3.7 ± 1.0 seconds, which was significantly less than the normal mean of 12.0 ± 7.4 seconds ($p < .0001$, Mann-Whitney U test). The range of means for the time constant was 2.0 to 5.4 seconds, which overlaps with the lower fifth percentile of normal (4.2 seconds).

Figure 2C shows the distribution of SCEP in the patients with ototoxicity. Values for SCEP in patients were calculated from the mean of two OKAN decay curves: one to the left and one to the right. The mean SCEP in patients, 19.7° ± 6.2° (range,

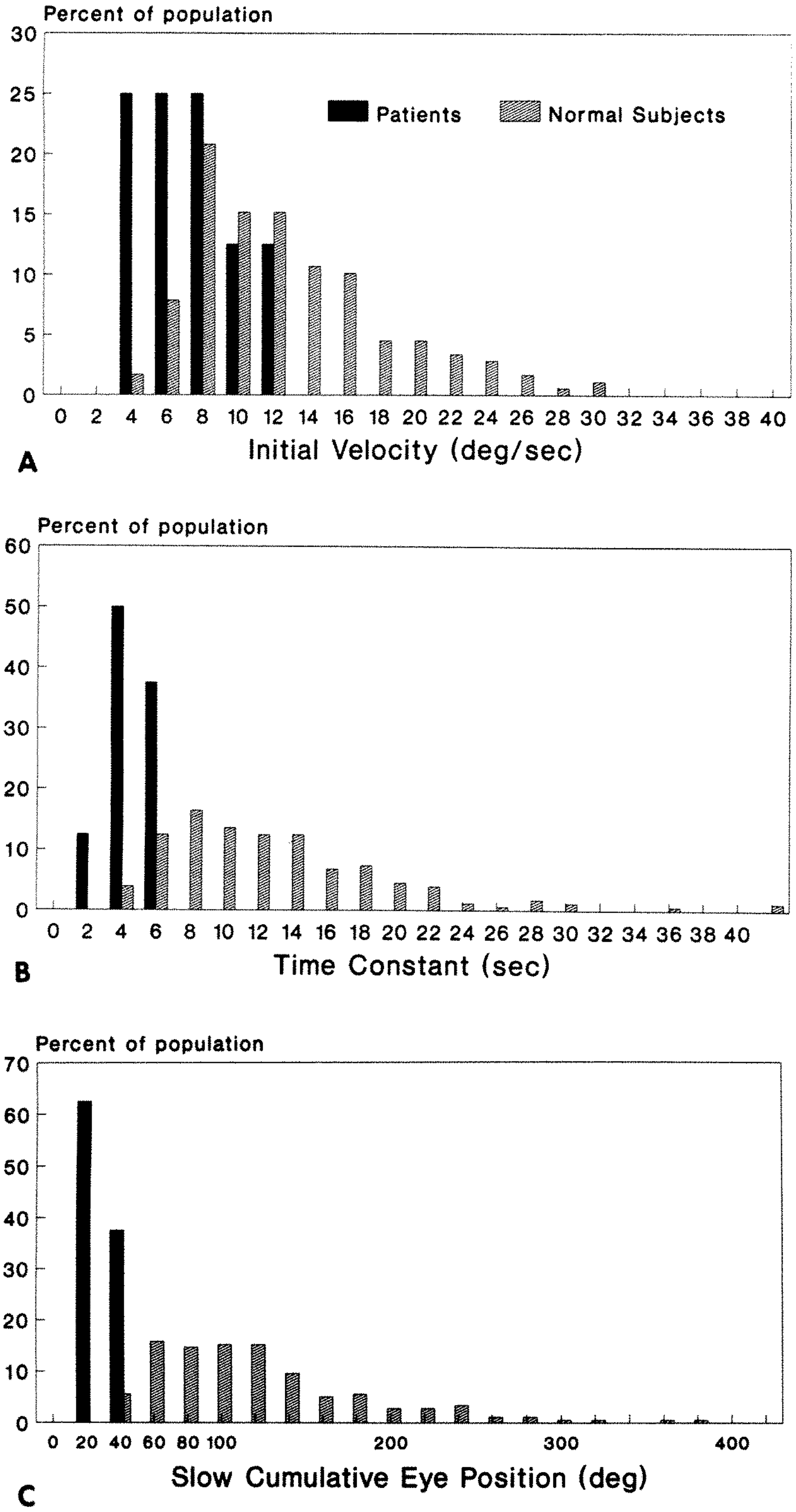

Fig 2. Distribution of A) optokinetic afternystagmus (OKAN) initial velocity, B) OKAN time constant, and C) OKAN slow-phase cumulative eye position.

12.5° to 31.5°), was significantly different from the mean SCEP in normal subjects, which was 112° ± 65° ($p < .0001$, Mann-Whitney U test). All patients had SCEP values less than the lower fifth percentile of normal subjects (40°).

DISCUSSION

Our data document that patients with oscillopsia and a history of ototoxic drug exposure have, both as a group and individually, significantly reduced OKAN as compared to normal subjects. The SCEP was the most sensitive measure of OKAN, followed by the time constant and the initial velocity. These findings confirm previous reports that OKAN is symmetrically reduced in conditions that impair peripheral vestibular function symmetrically,[2,7,8,12] and extend this observation to a specific subgroup.

From a practical point of view, OKAN is a highly sensitive but nonspecific indicator of bilateral vestibular loss. It is nonspecific since patients with Wallenberg's syndrome and multiple sclerosis may also have reduced OKAN.[13] Whether or not there are other conditions that abolish OKAN is as yet unknown. Accordingly, OKAN might be most useful to clinicians in confirming the diagnosis of ototoxicity. When caloric responses are absent, rotatory chair testing is usually necessary to confirm decrease or absence of vestibular function. The absence of OKAN in a patient complaining of oscillopsia is an additional confirmation of bilateral vestibular paresis.

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FIRST INTERNATIONAL SKULL BASE CONGRESS

The First International Skull Base Congress will be held June 14-20, 1992, in Hanover, Germany. For further information, contact Madjid Samii, MD, Professor and Chairman of Neurosurgery, Medical School Hanover, Neurosurgical Clinic, Hospital Nordstadt, Haltenhoffstr 41, D-3000 Hanover 1, Germany; phone 0049-(0)511-7638245 or 623151, FAX 0049-(0)511-7638606.

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PACING PARAMETERS OF THE CANINE POSTERIOR CRICOARYTENOID MUSCLE

SHIGERU KANO, MD
TOCHIGI, JAPAN

CLARENCE T. SASAKI, MD
NEW HAVEN, CONNECTICUT

The electrical pacing of laryngeal tissue consists of many uncharted parameters. We carried out several acute experiments in the canine model to narrow parametric ranges to serve future research and development in this field. Our findings were as follows. Stimulation intensities greater than 6 V caused tissue damage. Optimum stimulation frequency ranged from 60 to 90 Hz. Optimum pulse duration was 2.0 milliseconds. Biphasic stimulation reduced accumulation of electrical charge at the electrodes.

KEY WORDS — electrical pacing, posterior cricoarytenoid muscle.

INTRODUCTION

The larynx is a highly complex organ with three important yet mutually exclusive functions: protection of the lower airway, respiration, and phonation.[1] When the recurrent laryngeal nerves (RLNs) are damaged by surgical misadventure or trauma, life-threatening airway obstruction may result as the vocal folds assume adducted positions caused by unopposed cricothyroid muscles innervated by intact superior laryngeal nerves (SLNs).[2-6]

Several surgical procedures have been proposed to restore respiratory function by selectively removing laryngeal tissue[7-14] or by vocal fold lateralization.[15-18] However, no method has been judged completely satisfactory, because each compromises protective and phonatory functions. Since Horsley[19] reported his successful repair of an RLN transected in a gunshot injury in 1909, numerous surgical maneuvers on the nerves[20-35] and nerve-muscle pedicles[36] have been attempted with variable success due to the complex structure of the RLN[37] and misdirected neural regeneration.[38]

The possibility of electrical stimulation to restore original muscle function was first discussed by Liberson et al[39] in 1961. Since then, this technique has been applied successfully to many paralytic conditions of the diaphragm,[40] facial muscles,[41] and heart. Since 1977, when Zealear and Dedo[42] first reported the possibility of using this method for the larynx, many investigators have reported the feasibility of selective stimulation of intrinsic laryngeal muscle (specifically, the laryngeal abductors) as a therapeutic alternative in bilateral recurrent nerve paralysis to improve crippled laryngeal function.[43-50]

As the configuration of electrical pacing consists of many uncharted parameters, we carried out several acute experiments to narrow parametric ranges that could be used for future research and development in this field.

MATERIAL AND METHOD

Adult mongrel dogs (20 to 30 kg) were anesthetized with intravenous sodium pentobarbital 20 mg/kg. The paralyzed state was recreated by sectioning both RLNs. The right posterior cricoarytenoid (PCA) muscle was exposed by dividing the cricopharyngeus muscle and rotating the larynx 45°.

A stimulation electrode was newly designed to permit a preselected geographic surface area. A coated platinum-tungsten wire electrode of 0.002 in in diameter was spirally coiled after a calculated length of insulation coating was removed from its coiled portion, and the distal tip was bent back to form a hook (Fig 1). Thus, we could easily manufacture electrodes with exposed areas of 10 mm² and 7 to 10 mm in length. The hooked coiled wire electrode was placed inside a 21-gauge hypodermic needle with its hook outside the needle tip. Two needles were inserted parallel to each other with a distance

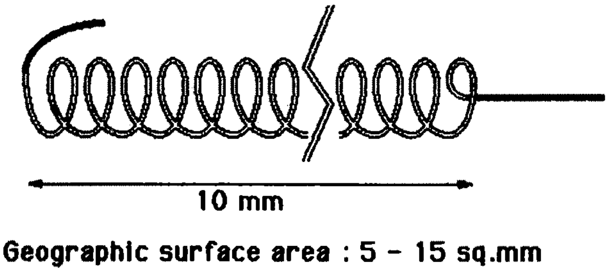

Fig 1. Coated platinum-tungsten wire of 0.002 in in diameter was spirally coiled after calculated length of insulation coating was removed from its coiled portion, and distal tip was bent back to form hook. Insulated portions (thick black lines) are located at distal end of wire (hook) and at proximal end of electrode connected to stimulation device.

From the Section of Otolaryngology, School of Medicine, Yale University, New Haven, Connecticut. Dr Kano is currently at the Department of Otolaryngology, National Tochigi Hospital, Tochigi, Japan. Supported by National Institutes of Health grant RO1-NS-23062, the McFadden Endowment, and the Keelips Fund. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Yale University.

REPRINTS — Clarence T. Sasaki, MD, Section of Otolaryngology, School of Medicine, Yale University, 333 Cedar St, New Haven, CT 06510.

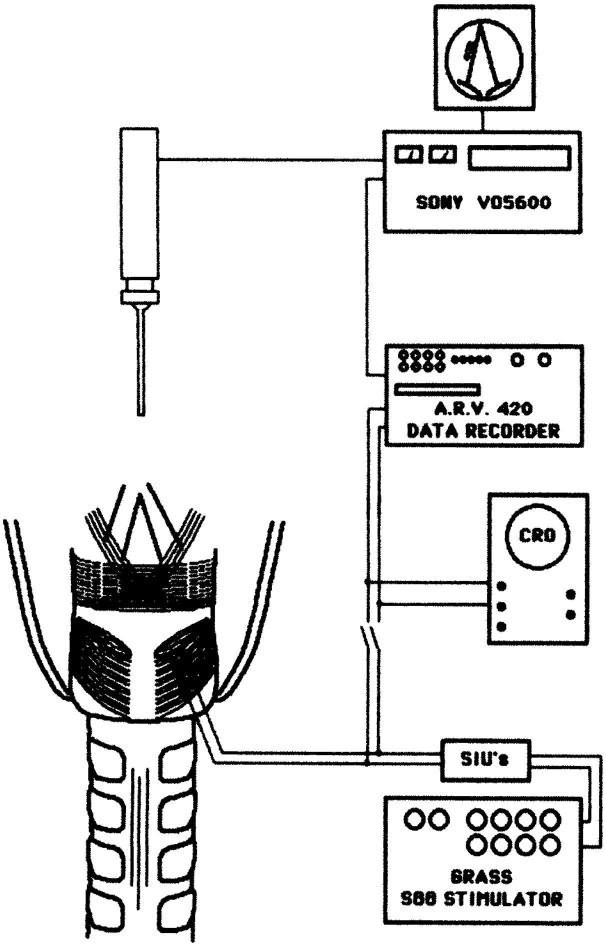

Fig 2. Posterior cricoarytenoid muscle was electrically stimulated with bipolar electrodes and use of biphasic waveforms. Vocal fold excursion was observed with videolaryngoscopy. Videocassette recorder and data recorder were used to store vocal fold movement and stimulation waveforms. CRO — cathode ray oscilloscope, SIU's — stimulation isolation units.

of 2 mm between them, crossing the midportion of the PCA muscle perpendicular to its fibers. Then the needles were carefully withdrawn to anchor the electrodes in the PCA muscle. The electrical field generated between the parallel electrodes was that of an ellipsoid perpendicular to the PCA muscle fibers.

The PCA muscle was electrically stimulated with biphasic waveforms by use of a Grass S88 stimulator and two isolation units. Experiments involved the comparison of two groups of preparations: 1) acutely sectioned RLN (control) and 2) acutely sectioned RLN plus intravenous pancuronium bromide (0.1 mg/kg), intended to exclude direct stimulation of neural tissues. The effects on vocal fold excursion were observed under three variable stimulation conditions in each experimental group: 1) 1 to 6 V (2.0 milliseconds' pulse duration), 2) 10 to 200 Hz, and 3) 0.2 to 4.0 milliseconds' pulse duration.

Through a suspension laryngoscope, vocal fold movement was observed by videolaryngoscopy. A marker of 1 x 4 mm was placed on the upper surface of the opposite vocal fold for calibration. This video system consisted of 1) Panasonic video camera WV 3600, 2) Sony videocassette recorder VO 5600, 3) Panasonic monitor BT-1300N, and 4) ARV data recorder model 420 (Fig 2).

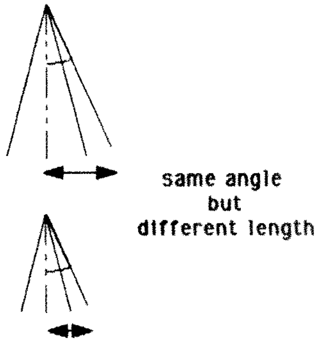

Fig 3. Schematic representation of vocal fold movement demonstrates that smaller glottis results in smaller horizontal excursion, although angle subtended from midline (dashed line) remains unchanged. This angle of abduction then becomes relevant measurement allowing comparisons across experimental animals.

Lateral excursion of the vocal fold in response to the electrical stimulation was measured as the angle subtended from the vertical midline of the glottis to the stimulated fold; this method eliminated inaccuracies caused by differences in vocal fold size. The angle obtained in this way then became the relevant measurement in estimating optimum stimulation parameters (Fig 3).

RESULTS

In initial experiments, stimulation intensity was examined up to 10 V. Although small increases in abduction were observed above 6 V, tissue damage around the electrode was found at these intensity levels (Fig 4). Thus, the safety range for stimulation intensity was determined to be ≤ 6 V.

In control experiments significant lateral excursion of the vocal fold was observed even at a lower intensity (2 V). Maximum abduction was obtained at frequencies ranging from 40 to 90 Hz, with only small differences observed among the measured intensity levels. From 10 to 30 Hz, vocal fold oscillation synchronous with the stimulation frequency was observed. As stimulation frequency increased, the amplitude of the oscillation decreased. From 40 to 90 Hz, vocal fold position remained stable, and very little oscillation was noted. However, the degree of abduction decreased when the frequency exceeded 90 Hz. These characteristics were observed at each intensity level, and no significant differences were found in the abduction amplitude (Fig 5).

By contrast, in the denervated model in which neuromuscular junction unit activity was completely blocked, no vocal fold movement was observed until the stimulation intensity approached 3 V. Lat-

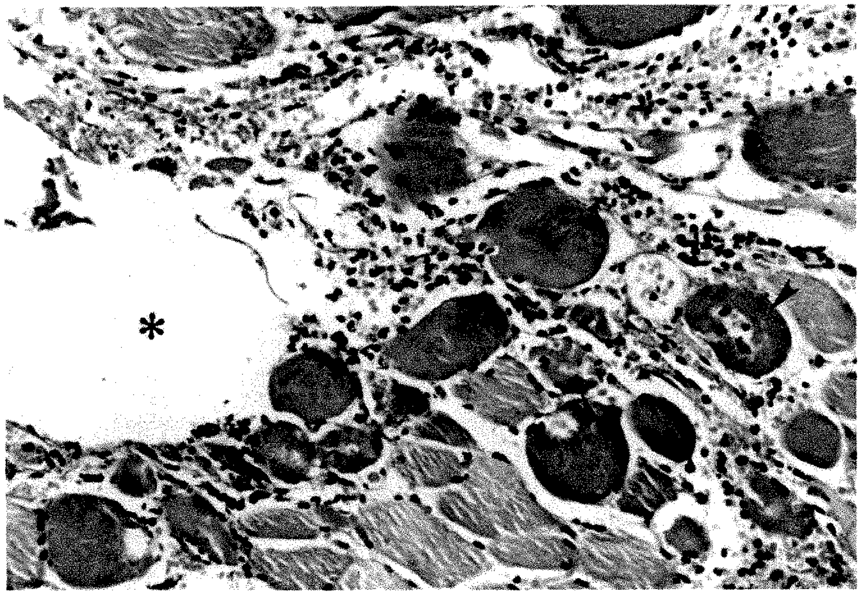

Fig 4. Around electrode track (asterisk) are several densely hyalinized muscle fibers, some of which show sarcoplasmic disintegration (arrowheads) (H & E, original x310).

eral excursion increased as stimulation intensity increased at each frequency. At every intensity level the largest movement was observed in the range of 60 to 90 Hz. At 10 and 20 Hz, vocal fold oscillations were noticed but were smaller than those found in the control experiment. Up to 60 Hz, abduction increased in proportion to the stimulation frequency, although it decreased again in the range over 90 Hz. This tendency was observed at each intensity level.

Pulse duration was increased from 0.2 to 4.0 milliseconds. Intensity was set at 6 V, while frequency was varied between 10 and 70 Hz. At 0.2 and 0.5 milliseconds' duration, no vocal fold movement was observed. At 1.0 millisecond's duration, small movement was observed under magnified videolaryngoscopy. Significant arytenoid movements were observed at 2.0 and 4.0 milliseconds' pulse duration (Fig 6).

DISCUSSION

Despite the uniform size and weight of our experimental dogs, we noted a wide variation in the size of the larynx. Therefore, the amount of lateral excursion of the vocal fold among different laryngeal sizes required a means of standardization. We thus used the angle subtended between the abducted fold and a vertical line passing through the anterior commissure. By using this parameter, we could measure degree of excursion directly from the video monitor or video print. Because this parameter was independent of glottic size, it could be used across all subjects.

Since the described experimental conditions involved a relatively fixed resistance across PCA tissue and widely varying resistances across adjacent tissues, the preferred measure of stimulus intensity in volts was used.

Maximum abduction was obtained at 60 Hz when the neuromuscular junction was blocked, compared to 40 Hz in unblocked control experiments. In the latter case, vocal folds were observed to be maximally abducted. Although the subtended angle at this point was about 30° and less than the reported range of motion of the cricoarytenoid joint in the horizontal plane (35°),[51,52] we considered this difference insignificant.

Vocal fold oscillations found at stimulation frequencies of 10 and 20 Hz can be clearly explained from physiologic properties of the PCA muscle. The interval between each stimulation can be calculated at 100 and 50 milliseconds, respectively. According to Martensson and Skoglund,[53] the average contraction time of the PCA muscle is 30 milliseconds, ranging from 25 to 35 — a range that is shorter than the stimulation interval we used. Thus, in these ranges contraction of the PCA muscle pursues every stimulus, producing oscillatory movement of the vocal cord.

In control experiments, isometric tensions would have increased after the stimulation frequency exceeded the contraction time of the PCA muscle.[54] As Burke et al[55] described, striated muscles are made up of type I and type II fibers, as confirmed by adenosinetriphosphatase histochemical studies. Type I fibers are thought to correspond to slow twitch fibers, and type II to fast twitch.[56-59] There are strong correlations between the ratio of these two fiber components and their contraction properties. The PCA and cricothyroid muscles are characterized by contraction times longer than those of the thyroarytenoid or lateral cricoarytenoid muscles. Type II fibers predominate in the latter muscle groups (80% or more), characterized by contraction times of about 15 milliseconds.[57] In the PCA muscle the proportion of type II fibers is smaller than that found in either the thyroarytenoid or lateral cricoarytenoid muscles.[57-60]

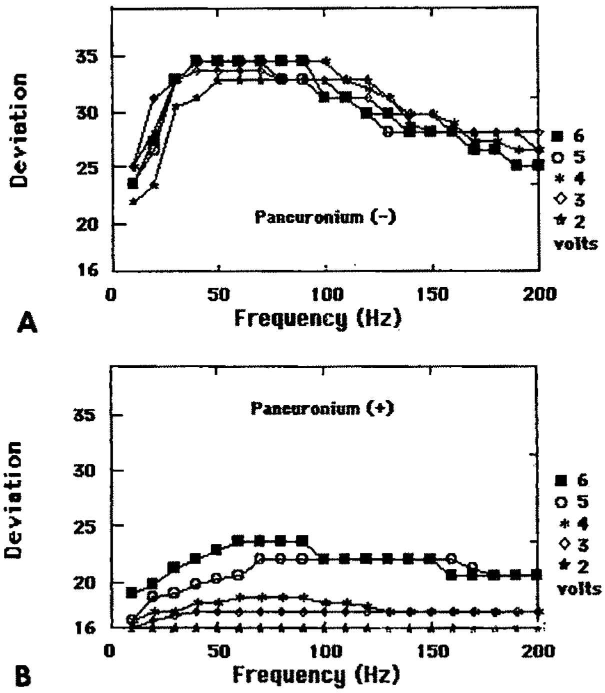

Fig 5. Stimulation intensity is varied from 2 to 6 V with A) unblocked neuromuscular junctions and B) blocked neuromuscular junctions. Note that optimum vocal fold deviation in degrees occurs between 40 and 90 Hz with pulse width of 2 milliseconds in unblocked state (A). After pancuronium bromide (B), optimum vocal deviation occurs above 5 V, between 60 and 90 Hz, with 2 milliseconds' pulse width.

From these differences the following explanation is possible. When the stimulation frequency is below 30 Hz, both slow and fast twitch fibers contract to produce vocal fold oscillation. From 30 to 40 Hz, slow fibers gradually develop tonic contraction, while fast fibers continue to twitch. Contraction power generated during the twitch is smaller than that produced by tonic contraction.[56] As the stimulation frequency increases, the fast twitch finally produces tonic contraction (observed at 60 Hz). From this point no additional contraction power is generated. Since all the fibers are now in tonic contraction, no oscillations are noted.

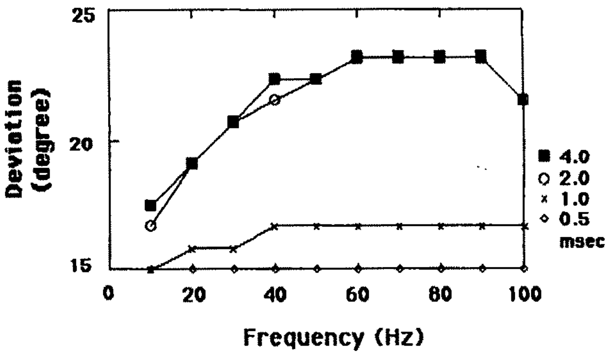

Fig 6. Optimum vocal fold deviation occurs between 60 and 90 Hz at pulse widths of 2.0 to 4.0 milliseconds in denervated state (stimulation intensity, 6 V).

The decrease of abduction at higher stimulation frequencies can be explained on the basis of the physiologic properties of the PCA muscle as studied by Martensson and Skoglund.[53] The reduction of tension at higher stimulus rates can be partly attributed to a decrease in action potential amplitude that may occur even during the rising phase of the tetanic contraction curve.

Significant findings of this study include the following: 1) stimulation intensity limited to 6 V avoids tissue damage around electrodes,[61] 2) optimum stimulation frequency ranges from 60 to 90 Hz, 3) optimum stimulation duration is 2.0 milliseconds, and 4) biphasic stimulation reduces the accumulation of electrical charge at the electrodes, preventing their eventual corrosion.[62,63] These observations constitute an attempt to narrow parametric ranges for future research in an important field of clinically relevant investigation.

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ARACHIDONIC ACID METABOLITES IN MIDDLE EAR EFFUSIONS OF CHILDREN

LINDA BRODSKY, MD
BUFFALO, NEW YORK
HOWARD FADEN, MD
BUFFALO, NEW YORK
JOEL BERNSTEIN, MD
BUFFALO, NEW YORK
JOHN STANIEVICH, MD
BUFFALO, NEW YORK
GIOVANNA DECASTRO, MD
ROME, ITALY
BENJAMIN VOLOVITZ, MD
PETAH-TIQVA, ISRAEL
PEARAY L. OGRA, MD
BUFFALO, NEW YORK

Middle ear effusions (MEEs) from 78 children (98 ears) with otitis media were examined for products of arachidonic acid (AA) metabolism, including leukotrienes B4, C4 , D4, and E4 and prostaglandins D2 and E2, by high-performance liquid chromatography. Leukotrienes B4 and D4 were recovered most frequently: 59% and 54%, respectively. Leukotriene B4 was found in highest concentration, 1.29±3.46 ng/0.1 mL. The concentrations of leukotrienes B4 ($p<.03$), C4 ($p<.01$), and E4 ($p<.02$) were significantly higher in culture-positive than in culture-negative MEEs. Neither the concentration nor the type of AA metabolite correlated with bacterial species isolated, chronicity of effusion, age of subject, or consistency of MEE. These data suggest that the AA metabolites are synthesized relatively frequently during otitis media of childhood. Leukotriene B4 is the most frequently detected AA metabolite in MEEs and is highly associated with the presence of viable bacteria.

KEY WORDS — arachidonic acid, leukotrienes, middle ear effusion, otitis media, prostaglandins.

INTRODUCTION

Otitis media with effusion (OME) is a ubiquitous disease, with up to 65% of children experiencing at least one ear infection by the second birthday.[1] The impact of OME on the health of children, as well as the cost to society, is enormous. Despite the extent of the problem, the pathogenesis of OME remains incompletely understood.

Multiple factors may contribute to the development of OME. Eustachian tube dysfunction along with upper respiratory tract infection are important in the pathogenesis of OME.[2] Children with immunologic disorders may be more susceptible to OME; however, the vast majority of children with recurrent disease have no identifiable immunologic problem.[3]

The role of arachidonic acid (AA) metabolites in the production and persistence of effusions has received recent attention. Both leukotrienes (LTs) and prostaglandins (PGs) are derived from phospholipids of cell membranes.[4] Phospholipase releases AA from the cell membrane phospholipids. Arachidonic acid is then metabolized by two pathways: cyclooxygenase, resulting in the PGs and thromboxane, and lipoxygenase, resulting in hydroxyeicosatetraenoic acid and the LTs. The proposed effects of LTs and PGs include chemotaxis of polymorphonuclear cells (PMNs), eosinophils, monocytes, macrophages and fibroblasts, increased vascular dilatation and permeability with plasma exudation from posterior capillary venules, constriction of smooth muscle, bone absorption, edema, and pain (Table 1). Products of inflammation such as the LTs and PGs have been detected in clinical as well as in experimental middle ear effusions (MEEs).[4] Recent work (unpublished data) from our own laboratory has demonstrated the importance of the immune response to middle ear pathogens in the release of leukotriene B4 from neutrophils.

To date, most therapeutic options in OME have focused on altering the bacteriologic factors that affect the development of OME. Understanding the role of biochemical mediators of inflammation may be important in developing alternative and/or supplemental forms of therapy. The present report characterizes the pattern of synthesis of various AA metabolites in middle ear disease and correlates their presence and concentration to the clinical history, fluid characteristics, and type of bacterial species present in MEE.

TABLE 1. EFFECTS OF ARACHIDONIC ACID METABOLITES

Metabolites	*Effects*
Leukotriene B4	Chemotaxis polymorphonuclear cells and eosinophils, increased vascular permeability, hyperalgesia
Leukotriene C4	Smooth muscle contraction, exudation of plasma from capillaries
Leukotrienes D4 and E4	Unknown
Prostaglandin D2	Regulation of collagenase activity by macrophages
Prostaglandin E2	Vasodilation, edema, pain, bone resorption, chemotaxis monocytes

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From the Departments of Otolaryngology (Brodsky, Bernstein, Stanievich) and Pediatrics (Brodsky, Faden, Bernstein, DeCastro, Volovitz, Ogra), State University of New York at Buffalo, School of Medicine, Children's Hospital of Buffalo, Buffalo, New York. Supported in part by grant HD 19679 from the National Institutes of Health/National Institute of Child Health and Human Development.

REPRINTS — Linda Brodsky, MD, Dept of Otolaryngology, Children's Hospital of Buffalo, 219 Bryant St, Buffalo, NY 14222.

METHODS

General Design. A longitudinal (prospective) study of otitis media in children who ranged in age from birth to 5 years was being conducted at The Children's Hospital of Buffalo (National Institute of Child Health and Human Development grant 19679). Seventy-eight of the 200 children enrolled in the study served as the basis for this study. Children were examined four times per year during healthy visits and when ill with ear infections. The diagnosis of otitis media was established by pneumatic otoscopy and tympanometry. Otitis media was clinically classified as acute (symptomatic, bulging tympanic membrane, and present less than 3 weeks), subacute (retracted tympanic membrane present 3 weeks to 3 months), and chronic (retracted tympanic membrane present more than 3 months). Tympanocenteses were performed and MEEs collected with an Alden-Senturia aspirator. The fluid consistency was characterized as purulent, mucoid, serous, or seromucinous.

Fluid Analysis. The MEE was diluted up to a volume of 2 mL in phosphate-buffered saline. An aliquot of the fluid was cultured aerobically. The fluid was centrifuged at 2,500 rpm at 4°C for 10 minutes to remove cellular elements, and the supernatant was frozen at −70°C. The cell pellet was resuspended in 1 mL of phosphate-buffered saline for total white blood cell and differential cell counts.

Leukotriene and Prostaglandin Analysis. The LTs and PGs were extracted from MEE samples with minor modification of a previously described method.[5] All reagents used in this procedure were of high-performance liquid chromatography (HPLC) grade (Aldrich Chemical Co, Milwaukee, Wis). A 0.1-mL volume of MEE was mixed with four volumes of ice-cold methanol, incubated for 4 hours on ice, and centrifuged at 2,500 rpm at 4°C for 20 minutes. After vacuum extraction to dryness in a rotary evaporator, the residue obtained was dissolved in 4 mL of 20% methanol and applied to an octadecylsily silica cartridge (Sep-Pak C_{18}; Millipore Waters Corp, Millford, Mass), prewashed with 10 mL of water, and activated with 10 mL of methanol. Samples were then eluted with 10 mL of a 70% solution of methanol. The sample thus prepared was subjected to vacuum extraction to dryness and the residue was redissolved in 0.5 mL of 30% methanol. The sample was then injected into a C_{18} reverse-phase column (Beckman, San Roman, Calif), eluted isocratically at a flow rate of 1 mL/min in an HPLC system (Pharmacia, Piscataway, NJ) with a solvent system of methanol/water/acetic acid (72/28/1, vol/vol), and adjusted to pH 5.5 by ammonium hydroxide. The eluate was monitored at 280 nm by a wavelength spectrometric detector. Leukotrienes could be separated from PGs reasonably well at 280 nm, even through this was not optimal. Leukotrienes were recovered at a rate of approximately 86% in the HPLC system. Radioimmunoassay was used to confirm the specific AA metabolites. Metabolites such as thromboxane, B2, and 6-keto-PGF_2 were not determined. Each sample was tested in duplicate. Purified preparations of LTB_4, LTC_4, LTD_4, LTE_4, PGD_2, and PGE_2 (a generous gift of J. Rokach, Merck Frost, Montreal, Canada) were employed as standards and tested in parallel with the sample. The presence of LTB_4 in materials determined to be positive by HPLC was verified by a specific radioimmunoassay (New England Nuclear, Boston, Mass) as previously described.

Statistical Analysis. The data were analyzed with the SPSSX statistical package. Significance was determined at the $p = .05$ level. Pearson's correlation coefficients, Student's *t* test for independent variables, and analysis of variance were used where appropriate.

RESULTS

Study Population. Seventy-eight children (98 ears) were evaluated in the present report. They ranged in age between 5 and 70 months (mean, 22.8; SD, 15.8). Fifty (64%) children were male and 28 (36%) were female. The number of total episodes of otitis media per child ranged from 1 to 16 (mean, 6.4; SD, 4.8). The children were seen during acute (44%), subacute (22%), and chronic (34%) episodes of otitis media.

Middle Ear Effusions. The MEEs were characterized as purulent in 32%, mucoid in 30%, serous in 20%, and seromucinous in 18%. The total white blood cell count of the fluids ranged between 0 and 34×10^5 cells/cm^3 (mean, 5.1×10^5 cells/cm^3; SD, 8.6×10^5 cells/cm^3). The mean ± SD differential cell count revealed 69.4% ± 22.1% PMNs and 30.4% ± 22.7% mononuclear cells. The total white blood cell count and proportion of PMNs were significantly higher in purulent MEE than in mucoid ($p < .001$) or serous ($p < .001$) MEEs.

Bacteria were recovered in 77.1% of the 103 MEEs; 22 (22.9%) of the MEEs were sterile. Typical ear pathogens were isolated in 42.6% of the MEEs: nontypeable *Hemophilus influenzae* was isolated in 18 (18.8%), *Streptococcus pneumoniae* in 16 (16.6%), and *Branhamella catarrhalis* in 16 (16.6%). Coagulase-negative staphylococci were recovered in 23 (24.0%), and other typical nonpathogenic organisms such as diphtheroids, *Neisseria* species, and *Streptococcus viridans* were isolated in 44 (45.8%). Twenty-eight (36%) of the culture-positive MEEs harbored multiple bacterial isolates. Common ear pathogens (nontypeable *H influenzae, S pneumoniae*, and *B catarrhalis*) were isolated significantly more frequently from purulent fluid than from mucoid fluid ($p < .001$). Similarly, the PMN count was significantly greater in MEEs

TABLE 2. CONCENTRATION OF ARACHIDONIC ACID METABOLITES IN 98 MIDDLE EAR EFFUSIONS

	LTB4	*LTC4*	*LTD4*	*LTE4*	*PGD2*	*PGE2*
Range	0-21.0	0-5.0	0-9.2	0-8.8	0-10.0	0-8.0
Mean ± SD	1.3±3.5	0.5±1.0	1.0±1.6	0.7±1.5	1.2±2.4	0.6±1.5
Median	0.3	0.0	0.1	0.0	0.0	0.0
% Positive	59	37	54	49	37	27

Units are nanograms per 0.1 mL.
LT — leukotriene, PG — prostaglandin.

infected with nontypeable *H influenzae, S pneumoniae*, and *B catarrhalis* than with other organisms or no organisms ($p<.001$).

The presence of AA metabolites in 98 MEEs is listed in Table 2. Leukotrienes B4 and D4 were recovered most frequently: 59% and 54%, respectively. The mean ± SD concentrations of LTB4, PGD2, and LTD4 were greatest: 1.3±3.5 ng/0.1 mL, 1.2±2.4 ng/0.1 mL, and 1.0±1.6 ng/0.1 mL, respectively. However, the median values for LTB4 (0.3 ng/0.1 mL) and LTD4 (0.1 ng/0.1 mL) reflected their more frequent incidence of recovery. When AA metabolites were compared in culture-positive and culture-negative MEEs, LTB4 ($p<.03$), LTC4 ($p<.01$), and LTE4 ($p<.02$) were all significantly elevated in the culture-positive fluids regardless of the bacteria isolated (Table 3). Statistical analysis demonstrated that MEEs were more frequently culture-positive in older children (22.9 months) than in younger children (16.9 months) ($p<.05$). Statistical analysis revealed no significant correlation between age and AA metabolite concentration in MEE. In addition, there were no differences in concentration of AA metabolites recovered in relation to the clinical presentation (acute, subacute, or chronic) or to the consistency of the fluid (serous, mucoid, purulent, or seromucinous).

DISCUSSION

Middle ear effusions represent the local inflammatory response to an infection in a normally sterile region of the upper respiratory tract. The composition of the fluid is complex and consists of the cellular products of bacteria and inflammatory cells, fluids from plasma, and the local mucosal reaction. The current study confirms the presence of several AA metabolites in MEEs, in particular LTB4 and LTD4, and correlates the production of these mediators of inflammation with the existence of viable bacteria.

Metabolites of AA were first detected in MEEs in 1975 and 1976.[6,7] Subsequently, several reports from Jung et al[4,8-10] demonstrated a range of AA metabolites in chinchilla experimental MEEs as well as human clinical specimens. Recent studies suggest that products of the lipoxygenase pathway may be more important in the pathogenesis of OME than products of the cyclooxygenase pathway.[4,9] In the present study LTB4, LTD4, and PGD2 were found most frequently and in highest concentrations. Jung's[4] finding of increased concentrations of AA metabolites in MEEs from younger children was not confirmed in this study. Similarly, differences in AA metabolites based on clinical stage of disease (acute, subacute, and chronic) of fluid consistency were not detected in the present study, and therefore, using the level of AA metabolites to define the chronicity of disease may not be accurate. The prospective nature of this study or differences in the definition of the clinical diagnosis or consistency of effusion (44% "acute," 32% "purulent," and 77% culture-positive in the present study) may account for these differences.

The production of LTB4 has been linked to the degree of inflammation and to the presence of viable bacteria.[4,9] In the present report, LTB4, LTC4, and LTE4 were all present in significantly higher concentrations in culture-positive MEEs regardless of the bacterial species present. In vitro studies with *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa*, and *Proteus* species have demonstrated stimulation of LTB4 release from leukocytes.[11-15] Products from bacterial metabolism such as endotoxin, hemolysins, and alpha toxins appear to be the bacterial by-products responsible for the activation of the AA metabolic pathways.[12,13,16-18] In certain situations, opsonization of the bacteria and subsequent uptake of the bacteria by the neutrophil is sufficient to cause the cell to release LTB4.[11,15] These data help to explain the importance of the relationship between the presence of viable bacteria and increased release of leukotrienes in MEEs. Treatment with antibiotics (bacterial killing) as well as with anti-inflammatories may reduce the concentration of AA metabolites in the MEEs. Those anti-inflammatory agents that are effective in the lipoxygenase pathway may prove to be most efficacious.

In conclusion, the present study supports an im-

TABLE 3. ARACHIDONIC ACID METABOLITES IN 69 CULTURE-POSITIVE VERSUS 22 CULTURE-NEGATIVE MIDDLE EAR EFFUSIONS

	Culture-Positive (n = 69)	*Culture-Negative (n = 22)*	*p Value*
LTB4	1.49±3.90	0.42±0.63	<.03
LTC4	0.65±1.10	0.19±0.51	<.01
LTD4	1.00±1.44	0.59±1.07	NS
LTE4	0.74±1.45	0.25±0.54	<.02
PGD2	1.22±0.24	1.10±1.26	NS
PGE2	0.58±1.40	0.79±2.00	NS

Values are mean ± SD concentrations in nanograms per 0.1 mL.
LT — leukotriene, PG — prostaglandin, NS — not significant.

portant role for both LTs and PGs in the pathogenesis of otitis media. The presence of viable bacteria appears to correlate to significantly higher levels of LTB4, LTC4, and LTE4 in MEEs. Future studies should be directed toward identification of the specific stimuli responsible for AA metabolite production, the AA metabolite most important for the persistence of MEEs, and the therapeutic intervention that eliminates this process. The study of serial effusions in the same subjects will be helpful.

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Ann Otol Rhinol Laryngol 100:1991

MIDDLE EAR FLUID LYSOZYME SOURCE IN EXPERIMENTAL PNEUMOCOCCAL OTITIS MEDIA

NAOBUMI NONOMURA, MD
G. SCOTT GIEBINK, MD
TERUHIKO HARADA, MD
DANIEL ZELTERMAN, PHD
STEVEN K. JUHN, MD
MINNEAPOLIS, MINNESOTA

Middle ear infection with *Streptococcus pneumoniae* is important in the pathogenesis of acute and chronic otitis media, and lysozyme in middle ear fluid (MEF) is an important inflammatory mediator in this disease. To determine the source of lysozyme during the early period of acute pneumococcal otitis media, chinchillas were irradiated to induce neutropenia, and their middle ears were inoculated with heat-killed, encapsulated pneumococci. The number of inflammatory cells and concentration of lysozyme were measured in MEF between 6 and 72 hours after inoculation. In pneumococcus-inoculated ears, the mean number of inflammatory cells but not lysozyme was significantly lower in MEF from irradiated animals than that from nonirradiated animals at 6 hours. Since lysozyme accumulated in MEF before the influx of inflammatory cells in irradiated animals, the initial release of this inflammatory mediator is most likely not from inflammatory cells; and mucosal epithelial cells, the only other known source of lysozyme in the middle ear environment, were the probable source induced by the direct stimulation of pneumococci. Inflammatory cells may contribute lysozyme later in the inflammatory response, since cellular and lysozyme concentrations in irradiated and nonirradiated animals were similar between 24 and 72 hours. These results suggest that future therapeutic interventions to limit middle ear inflammation in acute otitis media may need to recognize the direct action of pneumococcal cells or their envelope components on middle ear epithelium.

KEY WORDS — lysozyme, neutropenia, otitis media, pneumococcus, *Streptococcus pneumoniae*.

INTRODUCTION

Pneumococcal middle ear infection is important in the pathogenesis of acute and chronic otitis media, and the disease is characterized by an early accumulation of lysozyme, serum proteins, and inflammatory cells and later accumulation of arachidonic acid metabolites in middle ear fluid (MEF).[1,2] An increased concentration of lysozyme in the MEF from otitis media patients and in otitis media animal models has been reported by many investigators,[3-6] and the concentration of this hydrolase is viewed as a reflection of inflammatory severity.

Lysozyme is an important component of inflammation and has direct bacteriolytic activity and negative feedback modulation on the inflammatory response, an effect that inhibits polymorphonuclear leukocyte (PMNL) chemotaxis.[7-9] We hypothesized that MEF lysozyme is derived not only from MEF inflammatory cells but also from middle ear epithelium, and that inflammatory responses are generated and modified by inflammatory cells and humoral factors as well as mediators released from the mucosa. Revealing the source of MEF lysozyme in otitis media is important in understanding mucosal defense mechanisms and in developing interventions to prevent chronic otitis media. We sought to determine the source of MEF lysozyme during the early period of inflammation in pneumococcal otitis media by producing neutropenia in the otitis media chinchilla model using irradiation before pneumococcus inoculation.

MATERIALS AND METHODS

A total of 18 healthy 1- to 2-year-old chinchillas weighing 400 to 600 g with normal middle ears (ascertained by otoscopy and tympanometry) were used for this experiment. After the animals were anesthetized with ketamine hydrochloride (30 mg/kg), 12 chinchillas were irradiated with 10 Gy and 6 were irradiated with 8 Gy by means of a Phillips RT 250 X-ray machine (tube to surface distance was 60 cm; power was 250 kV and 15 mA; filter was 0.35 mm^3; cone was 50/24 x 20; and dose rate was 0.954 Gy/min). The radiation field was defined below the neck by shielding the head with a lead plate to avoid irradiating the middle ear and upper respiratory mucosa. The nonirradiated control group of 90 chinchillas has been previously reported.[1]

Four days after irradiation, eustachian tube obstruction with Silastic sponge was performed,[10] and 1 day later 10^8 log-phase, heat-killed type 7F pneumococci in 0.5 mL of phosphate-buffered saline (PBS) pH 7.4 were inoculated in the hypotympanic bulla of each right ear; 0.5 mL PBS without bacterial cells was inoculated into the opposite middle ear. Control animals were operated on and inocu-

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From the Otitis Media Research Center (all authors), the Departments of Otolaryngology (Nonomura, Giebink, Harada, Juhn) and Pediatrics (Giebink), School of Medicine, and the Biostatistics Division, School of Public Health (Zelterman), University of Minnesota, Minneapolis, Minnesota. Supported by program project grant 8P50-CD-00133 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Minnesota.

REPRINTS — G. Scott Giebink, MD, Box 483 UMHC, 420 Delaware St SE, Minneapolis, MN 55455.

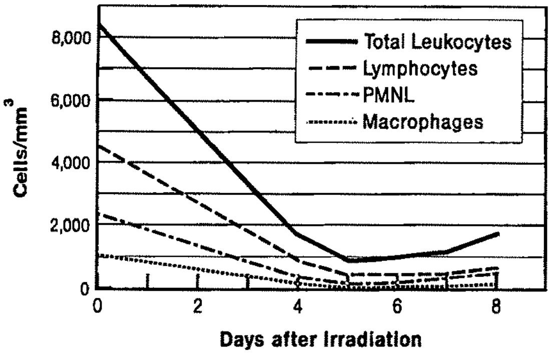

Fig 1. Geometric mean peripheral blood leukocyte counts after irradiation. Fifteen animals were sampled at 0, 4, and 5 hours; 14 at 6 and 7 hours; and 13 at 8 hours.

lated in an identical manner. Middle ear fluid was aspirated from the dorsal bulla at 6, 24, 48, and 72 hours after inoculation. Approximately 10 μL of aspirated fluid was cultured on 5% sheep blood agar and incubated for 48 hours in 10% carbon dioxide for routine bacterial identification.

Blood was sampled from an ear auricle vessel, and the number of leukocytes and differentiation were determined, as were cells in MEF. Remaining MEF was centrifuged and frozen for measurement of lysozyme using the Lysozyme Test Kit Quantiplates (Kallested, Chaska, Minn).

Data were analyzed by the two-tailed nonpaired *t* test. Only chinchillas whose MEF remained sterile throughout the study were included in the analysis. Ears suffering from tympanic membrane perforation or bleeding during paracentesis of fluid and ears with less than 50 μL of MEF were excluded from analysis; therefore, the number of ears analyzed at each time point varied.

RESULTS

Irradiation induced severe leukopenia with a rapid decline in peripheral blood leukocytes after irradiation (Fig 1). The absolute number of leukocytes was lowest (geometric mean [GM] = 241/mm^3) on the day of bacterial inoculation and remained less than 500/mm^3 during the study.

The GM inflammatory cell concentration in MEF from irradiated animals 6 hours after pneumococcus inoculation was virtually nil (35/mm^3) and was comparable to the cell concentration in saline-inoculated control ears. In contrast, MEF from nonirradiated animals showed significant cell influx as early as 6 hours (207/mm^3) (Fig 2). At 24 hours, the GM number of inflammatory cells in MEF from pneumococcus-inoculated irradiated animals (2,543/mm^3) approached the level in MEF from pneumococcus-inoculated nonirradiated animals (5,089/mm^3); and this difference persisted at 48 and 72 hours. This finding suggests that killed pneumococci are strong chemoattractants for inflammatory cells. The inflammatory cell influx into MEF from irradiated animals between 24 and 72 hours after inoculation occurred despite severe peripheral blood leukopenia during this period. This finding suggests that pneumococci were potent chemoattractants for the few PMNLs remaining in marginal sites. The GM inflammatory cell concentrations in saline-inoculated ears of irradiated and nonirradiated animals were very low and not significantly different.

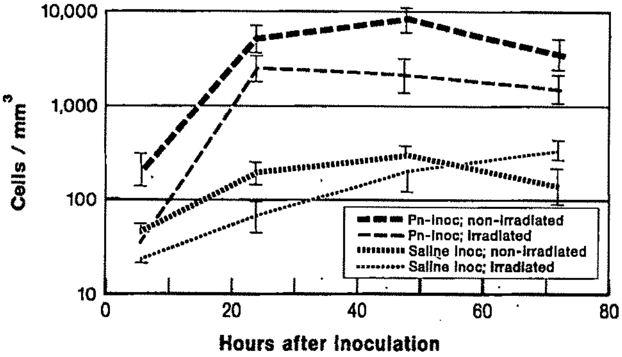

Fig 2. Inflammatory cells in middle ear fluid after middle ear inoculation of 10^8 heat-killed type 7F pneumococcus or sterile phosphate-buffered saline into previously irradiated and nonirradiated chinchillas. Geometric means and SEMs are shown. Numbers of samples obtained at 6, 24, 48, and 72 hours, respectively, were as follows: pneumococcus-inoculated/nonirradiated, 9, 10, 6, and 8; pneumococcus-inoculated/irradiated, 13, 11, 8, and 8; saline-inoculated/nonirradiated, 44, 28, 17, and 17; and saline-inoculated/irradiated, 11, 7, 5, and 5.

The GM concentrations of lysozyme in MEF were significantly higher in pneumococcus-inoculated ears of irradiated and nonirradiated animals than in saline-inoculated control ears of the respective irradiated and nonirradiated animals at all sampling times (Fig 3). In irradiated animals, lysozyme accumulation in MEF tended to be greater in pneumococcus-inoculated ears (2.34 μg/mL) than in saline-inoculated ears (1.63 μg/mL; $p = .09$) as early as 6 hours after inoculation, a time preceding the influx of inflammatory cells; this finding suggested that early lysozyme accumulation was derived from local sources (eg, middle ear epithelial cells) and not inflammatory cells.

Although the GM lysozyme concentration in MEF from saline-inoculated irradiated animals was twice the concentration in MEF from saline-inoculated nonirradiated animals, there was no significant difference between the GM lysozyme concentrations in MEF from pneumococcus-inoculated ears of irradiated and nonirradiated animals at any time (Fig 3).

DISCUSSION

Our results suggest that pneumococci in the middle ear space may directly stimulate middle ear epithelial cells to release lysozyme, since in neutropenic chinchillas lysozyme accumulated in MEF before the influx of inflammatory cells. Lysozyme present in MEF at subsequent times may have been derived from both epithelial and inflammatory cells,

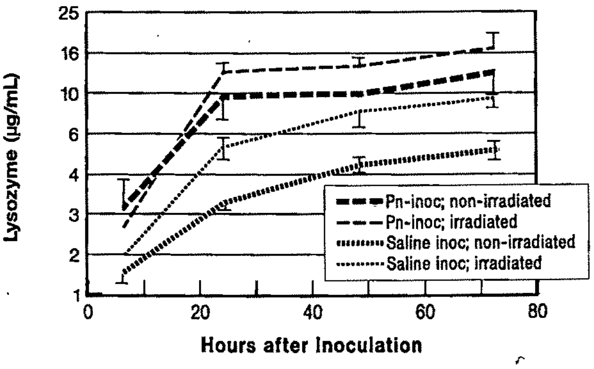

Fig 3. Lysozyme concentration in middle ear fluid after middle ear inoculation of 10^8 heat-killed type 7F pneumococcus or sterile phosphate-buffered saline into previously irradiated and nonirradiated chinchillas. Geometric means and SEMs are shown. Numbers of samples obtained at 6, 24, 48, and 72 hours, respectively, were as follows: pneumococcus-inoculated/nonirradiated, 9, 10, 6, and 7; pneumococcus-inoculated/irradiated, 13, 11, 9, and 8; saline-inoculated/nonirradiated, 43, 28, 15, and 17; and saline-inoculated/irradiated, 11, 8, 4, and 5. Differences between pneumococcus- and saline-inoculated ears of irradiated animals were significant at 6, 24, 48, and 72 hours (p values were <.10, <.01, <.01, and <.05, respectively). Differences between pneumococcus- and saline-inoculated ears of nonirradiated animals were also significant at 6, 24, 48, and 72 hours (p values were <.05, <.01, <.01, and <.05, respectively). Differences between pneumococcus-inoculated ears of irradiated and nonirradiated animals were not significant at any time. Differences between saline-inoculated ears of irradiated and nonirradiated animals were significant between 24 and 72 hours (p<.01).

since a strong correlation between the number of PMNLs and the concentration of lysozyme in MEF has been previously reported.[1]

The fact that irradiation alone caused increased release of lysozyme into MEF of saline-inoculated ears suggests that peripheral destruction of PMNLs and macrophages released lysozyme into serum with transudation into MEF. Although serum lysozyme was not measured to confirm this hypothesis, eustachian tube obstruction in the animal model is known to cause transudation of serum proteins into MEF.

The fact that lysozymes, which are α-1,4 glycan hydrolases with a range of biologic functions,[7] are present in high concentrations in MEF from patients with chronic otitis media with effusion and in MEF from otitis media animal models indicates their importance as inflammatory mediators in this disease.[3-6] In otitis media, lysozymes are derived from both middle ear epithelial cells and inflammatory cells (macrophages and PMNLs). An immunohistochemical localization study in normal chinchilla middle ear mucosa demonstrated lysozyme predominantly in the columnar epithelium of the transitional zone near the tympanic orifice of the eustachian tube; and a radioisotope incorporation study suggested that lysozyme-secreting cells were goblet cells.[9]

In PMNLs, lysozyme is found in primary (azurophil) and secondary (specific) granules. Bactericidal elements in primary granules also include myeloperoxidase, lysosomal hydrolases, and neutral serine proteases, in addition to lysozyme. Secondary granules contain collagenase and lactoferrin in addition to lysozyme, but not lysosomal hydrolases. Granule exocytosis can be induced by humoral stimuli, such as chemotactic factors, pyrogen, arachidonic acid metabolites, and phagocytic stimuli,[11-13] and injection of these lysosomal products from PMNLs into rat skin causes severe microvascular injury.[14] Neutral proteases from PMNLs degrade proteoglycan and collagen.[13] Therefore, PMNLs are a principal source of enzymes responsible for tissue damage in an inflammatory process.

Lysozymes are known to have bacteriolytic activity, cleaving the bond between *N*-acetyl muramic acid and *N*-acetyl glucosamine in cell wall peptidoglycan.[7] Although they are not very active against pathogenic bacteria, lysozymes in combination with other enzymes, such as lipases or proteases, can act synergistically to destroy certain bacteria.

Lysozymes have anti-inflammatory activity, as well. Human lysozyme may depress chemotaxis, oxidative metabolism, and superoxide generation by PMNLs, and may provide negative feedback to modulate the inflammatory response.[8] Therefore, an increase in the concentration of lysozyme in MEF may reflect the activated host defense mechanism.

These results suggest that future therapeutic interventions to limit middle ear inflammation may need to recognize the direct inflammatory action of pneumococci on middle ear epithelium.

ACKNOWLEDGMENTS — We are grateful to Drs Chan W. Song and Jyh-Chaerng Lim, Department of Therapeutic Radiology and Oncology, University of Minnesota Medical School, for irradiating chinchillas.

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LOW INCIDENCE OF POINT MUTATION AT CODON 12 OF K-*RAS* PROTO-ONCOGENE IN SQUAMOUS CELL CARCINOMA OF THE UPPER AERODIGESTIVE TRACT

TOSHIKAZU HIRANO, MD, PHD

PAUL E. STEELE, MD JACK L. GLUCKMAN, MD

CINCINNATI, OHIO

Forty-two cases of squamous cell carcinoma arising in the upper aerodigestive tract were examined to determine the incidence and type of point mutation in codon 12 of the c-K-*ras* gene by using the polymerase chain reaction and oligonucleotide hybridization techniques on DNA extracted from paraffin blocks. DNA sequencing, in addition, was performed in 4 cases. No point mutation was detected in codon 12 of c-K-*ras* in the 42 squamous cell carcinomas we examined. According to the results of DNA sequencing of 4 cases, codon 13 also revealed no point mutation. Thus, point mutational activation of codon 12 of c-K-*ras* oncogene is an uncommon event in human upper aerodigestive tract squamous cell carcinoma.

KEY WORDS — mutational activation, *ras* oncogene, squamous cell carcinoma.

INTRODUCTION

Several types of human malignant tumors have showed mutational activation and/or amplification and increased expression of *ras* proto-oncogene products.[1,2] The c-K-*ras* gene has been reported to show point mutation frequently in pancreatic cancer.[3] On the other hand, *ras* gene mutations are very rarely found in esophageal cancers[4] or hematopoietic tumors.[5] This contrast suggests that important differences in the frequency of activation of *ras* oncogenes may exist between tumors derived from different tissues or even between clinical and histopathologic subtypes of tumors derived from the same tissue. Data concerning the frequency and type of *ras* mutations in squamous cell carcinoma of upper aerodigestive tract mucosa have not been reported. In the present study, we extracted DNA from paraffin blocks and examined the incidence and type of point mutation at codon 12 in the c-K-*ras* gene using the polymerase chain reaction (PCR) to determine whether squamous cell carcinomas of the upper aerodigestive tract are associated with activation of *ras* genes by point mutation.

MATERIALS AND METHODS

Patients. Forty-two patients with squamous cell carcinoma of the upper aerodigestive tract were identified from a coauthor's records (J.L.G.). The patient information and tumor staging were obtained from these records. The patient population was 71% male and 29% female, with the age at diagnosis ranging from 38 to 79 years. The tumors were squamous cell carcinomas of the tongue (11), oral cavity (12), oropharynx (10), and larynx (9). Tumor staging (TNM) was performed according to the American Joint Committee on Cancer[6]: 5 cases of T1, 14 cases of T2, 13 cases of T3, and 10 cases of T4. Stage classification was as follows: 5 cases of stage I, 7 cases of stage II, 13 cases of stage III, and 17 cases of stage IV.

Extraction and Purification of DNA From Paraffin Blocks. The method of purification of DNA from formaldehyde-fixed and paraffin-embedded human tissue described by Goelz et al[7] was performed. A 5-μm section was cut from each block, stained, and examined for the location and extent of tumor. Each block was cut at 10-μm intervals for a total thickness of 150 to 300 μm with a clean razor blade that was discarded after each specimen (case) was cut. The sections were individually collected on glass slides and trimmed to remove tissue uninvolved by tumor. The tissue was suspended in TE9 (500 mmol/L Tris, 20 mmol/L ethylenediaminetetraacetic acid [EDTA], and 10 mmol/L sodium chloride [NaCl], pH 9.0) containing 1% sodium dodecyl sulfate (SDS) and 500 μg/mL proteinase K. After incubation at 48°C for 24 hours, the SDS was adjusted to 2% and proteinase K to 1,000 μg/mL. After further incubation at 48°C for an additional 48 hours, the samples were extracted with phenol-chloroform and then chloroform according to Goelz et al.[7] DNA was pelleted after the addition of ammonium acetate (0.3 mol/L) and 2.5 volumes of 95% ethanol, and the pellet was washed with 70% ethanol. The pellet was dried and resuspended in 100 μL of TE solution (3 mmol/L Tris and 0.2 mmol/L EDTA, pH 7.2).

Polymerase Chain Reaction. Oligonucleotides for 20-mer primers[8] were synthesized (Applied Biosystems). Target sequences of sample DNAs were amplified in vitro by using the GeneAmp DNA Amplification Reagent Kit (Perkin Elmer Cetus) by the polymerase chain reaction method.[9] Forty cycles of denaturation (95°C for 2 minutes), annealing

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From the Departments of Pathology and Laboratory Medicine (Hirano, Steele) and Otolaryngology and Maxillofacial Surgery (Gluckman), University of Cincinnati Medical Center, Cincinnati, Ohio.

REPRINTS — Jack L. Gluckman, MD, University of Cincinnati Medical Center, 231 Bethesda Ave, Cincinnati, OH 45267-0528.

NUCLEOTIDE SEQUENCE OF HYBRIDIZATION PROBES

Oligonucleotide Probes	*Codon 12*
GTT-GGA-GCT-GGT-GGC-GTA-G	Glycine
-CGT-	Arginine
-TGT-	Cysteine
-AGT-	Serine
-GCT-	Alanine
-GAT-	Aspartic acid
-GTT-	Valine

(55°C for 1 minute), and polymerization (72°C for 1 minute) were done on an automated heatblock (Coy Laboratory Products, Inc). The amplified DNA samples were subsequently run in 4% NuSieve agarose gels and transferred to nylon membranes (Schleicher & Schuell, Inc) by a Southern blot technique and fixed by baking at 80°C for 2 hours.

Oligonucleotide Hybridization. The filters were prehybridized overnight at 50°C in 3 mol/L tetramethylammonium chloride (TMAC), 50 mmol/L Tris-HCl buffer (pH 7.5), 2 mmol/L EDTA, 0.3% SDS, 100 μg/mL denaturated calf thymus DNA, and 5x Denhardt's solution. The filters were hybridized for 3 hours at 50°C with the series of 19-mer synthetic oligonucleotide probes (DuPont) shown in the Table. These probes are representative of the normal codon 12, as well as of all possible activating mutations affecting this codon. These oligonucleotide probes were labeled with [γ-^{32}P]ATP (Amersham, 3,000 Ci/mmol) by means of T4 polynucleotide kinase (ProMega). After hybridization, filters were washed twice in 2x SSPE (20 mmol/L sodium phosphate pH 7.4, 300 mmol/L NaCl, and 2 mmol/L EDTA) in 0.1% SDS for 30 minutes at room temperature. A final high-stringency wash was performed for 45 minutes at the melting temperature (Tm; 60°C or 62°C) in 3 mol/L TMAC, 50 mmol/L Tris-HCl buffer, 2 mmol/L EDTA, and 0.3% SDS. The filters were exposed to Kodak XAR film for 18 hours and 1 week at −70°C with DuPont Cronex intensifying screens.

DNA Sequencing. After producing single-stranded DNA with asymmetric PCR as described by McCabe,[10] Sanger DNA sequencing was done by means of the Sequenase version 2.0 (United States Biochemical Co) and [α-^{35}S]dATP. The 5′ PCR amplifier was used as the sequencing primer. The samples were run on a 4% polyacrylamide gel and the gel was exposed to Kodak XAR film for 12 hours at room temperature without an intensifying screen.

RESULTS

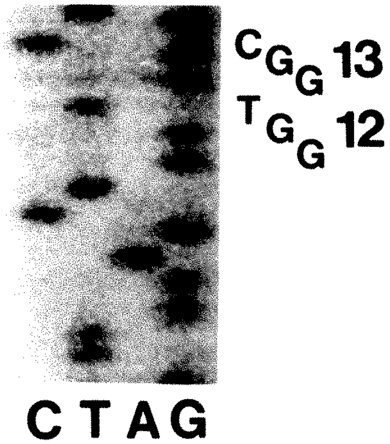
From the paraffin-embedded specimens of 42 squamous cell carcinomas, 20 to 120 μg of DNA was extracted. The DNAs were mainly of low molecular weight, ranging from 100 to 1,500 base pairs as assessed by agarose gel electrophoresis. These samples were adequate for the PCR-directed amplification of a 115-base pair segment that spanned the 12th and 13th codons of the c-K-*ras* gene.

Hybridization of these amplified DNAs with the synthetic oligonucleotides listed in the Table revealed reactivity only with the wild-type sequence oligonucleotide, indicating that no point mutation existed in codon 12 of the c-K-*ras* gene. Because of faint reactivity of four amplified DNAs with a mutant sequence oligonucleotide (seen only on the long autoradiographic exposure), DNA sequencing of the PCR products of these four samples was performed. The results showed no mutation in codon 12 or codon 13 (see Figure).

DISCUSSION

Ras oncogenes, which can be activated by chemical carcinogens, may provide a link between carcinogen exposure and the pathogenesis of tumors.[11,12] Activated *ras* genes with transformation activity have been detected in a wide variety of human cancers. With use of oligonucleotide probes to directly detect mutated *ras* genes,[13] a significant proportion of pancreatic carcinomas were found to be associated with point mutation in *ras* genes.[3,14] On the other hand, a half or less incidence of point mutation in K-*ras* genes has been reported in colon carcinoma,[15] lymphomas,[5,8] ovarian carcinoma,[16] lung carcinoma,[17] esophageal carcinoma,[4] and hepatocellular carcinoma.[18] This study attempted to assess comprehensively the frequency of activating mutations at the 12th codon of c-K-*ras* in squamous cell carcinoma of the upper aerodigestive tract. The method used, involving analysis by PCR and oligonucleotide hybridization, allows the screening of many cases even from formalin-fixed, paraffin-embedded samples and reveals qualitative data on the type of mutations.

Despite speculation that activating point mutations in codon 12 might be a result of a carcinogenic ingredient in tobacco smoke or chewing tobacco,[17] the results of this study indicate that mutations of



Nucleotide sequence of polymerase chain reaction product from representative tumor DNA. Codons 12 and 13 are labelled. C — deoxycytidine, T — deoxythymidine, A — deoxyadenosine, G — deoxyguanosine.

codon 12 of the c-K-*ras* gene are not or are extremely infrequently involved in the pathogenesis of squamous cell carcinoma in the upper aerodigestive tract. The results of this study, therefore, appear to invalidate the notion that *ras* activation represents a general mechanism involved with variable frequency in human malignancies. However, *ras* gene mutations can occur at a number of stages in transformation, either as initiating events or later as part of the evolution of neoplastic transformation.[8,19] It is possible that mutation of c-K-*ras* is an early event in the initiation of squamous cell carcinoma of the upper aerodigestive tract, but if so, our results suggest that such mutations are lost during clonal evolution of the neoplasm. Another possibility, that mutations at other *ras* codons (eg, codons 13 and 61) or other *ras* genes (N and H *ras*) may be specifically involved in the pathogenesis of these tumors, cannot be ruled out. Additional molecular genetic investigations will be required to clarify the role of *ras* activation in carcinogenesis of the upper aerodigestive tract.

ACKNOWLEDGMENT — The authors thank Professor Roger D. Smith for his great help and encouragement.

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IMAGING CASE STUDY OF THE MONTH

PLEOMORPHIC ADENOMA OF THE NASAL CAVITY

DAVID A. PRAGER, MD
WARREN L. BUCHALTER, MD
MICHAEL H. WEISS, MD
MORTON JACOBS, MD
NEW YORK, NEW YORK

CASE REPORT

A 55-year-old woman presented to the emergency room with epistaxis and nasal obstruction that had been present for a period of 1 year. On physical examination the blood pressure was 180/120. A fleshy mass filled the left nasal cavity, with extensive involvement of the palate. Epistaxis was controlled by nasal packing, and reduction of blood pressure was achieved with antihypertensive medication. A computed tomography scan with contrast was performed (see Figure).

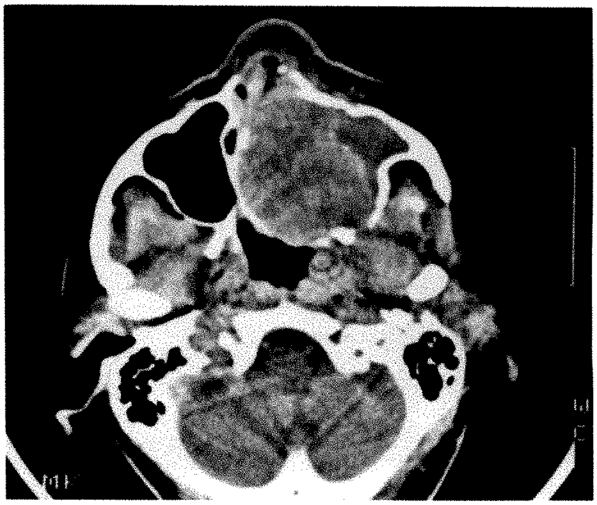
Biopsy revealed pleomorphic adenoma. Partial maxillectomy through a lateral rhinotomy approach was performed. The patient was rehabilitated with a dental prosthesis and is speaking and eating satisfactorily.

DISCUSSION

Pleomorphic adenoma (benign mixed tumor) most commonly affects the major salivary glands; the minor salivary glands are affected in only 8% of cases. Cases involving the nasal cavity are uncommon. Compagno and Wong,[1] in reviewing 40 such cases from the Armed Forces Institute of Pathology, found that most lesions originated from the septal mucosa. Most cases appear between the third and sixth decades of life, and there is no apparent race or sex predilection.

The typical presentation is that of a painless nasal mass or unilateral nasal obstruction. Less commonly, epistaxis is the chief complaint. Adequate local excision is the treatment of choice in all cases. Recurrences are rare.

The role of computed tomography in regard to tumors of the nasal cavity and paranasal sinuses is largely to determine anatomic borders as an aid to treatment planning. The pattern of bony alteration, whether or not the changes are expansile or destructive, provides the most reliable clue as to the benign or malignant character of the lesion. Expansivity suggests either a slow-growing malignancy (ie, adenoid cystic carcinoma, neuroma, or some melanomas) or a benign lesion (ie, inverting papilloma, angiomatous polyps, choanal polyps, or allergic polyposis). On the other hand, frank and aggressive permeative patterns of bone destruction are the hallmark of malignancy. Squamous cell carcinoma is the most common histologic type, comprising 80% of all nasosinal malignancies, the rest being lymphoma, esthesioneuroblastoma, and rarely sarcoma. The attenuation values of these tumors are an unreliable means of predicting histologic characteristics. Further confusing the issue is the presence of obstructed secretions and associated inflammatory tissue, which are frequent concomitants. The frequent overlap in density values often limits precise mapping of tumor margins.[2]



Axial computed tomogram showing heterogeneously enhanced tumor filling left nasal cavity, destroying lateral nasal wall, and extending into medial aspect of left antrum. Expansile nature of tumor is evident, with displacement of nasal septum from left to right up against right lateral nasal wall. Retained secretions are seen in left antrum, imaged as low-density material trapped behind tumor.

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From the Division of Otolaryngology, State University of New York, Health Science Center at Brooklyn (Prager, Buchalter), the Department of Otolaryngology, Manhattan Eye, Ear and Throat Hospital (Weiss), and the Department of Radiology, New York Hospital (Jacobs), New York, New York.
REPRINTS — Michael H. Weiss, MD, Dept of Otolaryngology, 210 E 64th St, New York, NY 10021.

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IMAGING CASE STUDY OF THE MONTH

BONE MARROW INVASION OF MICROCYSTIC ADNEXAL CARCINOMA

William T. C. Yuh, MD, MSEE
Duane C. Whitaker, MD
John D. Engelken
Kenneth D. Dolan, MD
Iowa City, Iowa

INTRODUCTION

Microcystic adnexal carcinoma (MAC) has been shown to be locally aggressive and invade deeply and extensively without clinically apparent findings. Direct bone invasion and neural spread through the mental foramen to involve and replace the bone marrow represent a new facet in the extent of local MAC aggressiveness. We report computed tomography (CT) and magnetic resonance imaging findings of a case of MAC with bone marrow involvement due to perineural extension through the mental foramen.

CASE REPORT

A 51-year-old man presented with a 5-year history of an asymptomatic, firm, slightly elevated, pale yellow nodule (0.5 cm) on the left side of the lower lip. There was no appreciable lymphadenopathy or other skin lesions and no history of exposure of the face to irradiation. Punch biopsy and subsequent wedge excision of the lip revealed a MAC with involvement of the surgical margins. The area was treated with 57.5 Gy of radiotherapy. Three years later, lip contracture and ulceration at the surgical site led to the diagnosis of MAC recurrence.

A CT scan (Fig 1) of the mandible showed a broad flat plaque of enhancing tissue on the left side of the lower lip and chin that merged with the adjacent portion of the mandible and on one cut seemed to be associated with a small scalloped focal area of bony erosive change. This area was thought to represent a possible extension of the lesion into the mandibular neural canal. No spread of the tumor to lymph nodes or bone marrow was visualized.

Magnetic resonance imaging (Fig 2) revealed a defect seen in the left side of the lower lip with absent signal on intermediate and T2-weighted images. There was decreased signal in the left middle

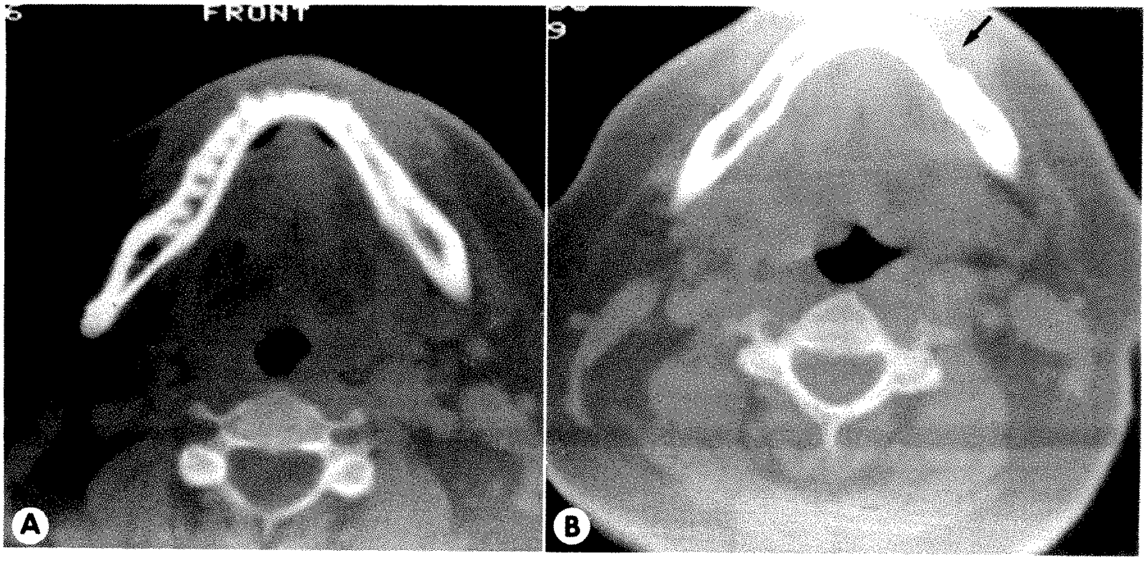

Fig 1. Axial computed tomograms with 0.8-cm slice thickness obtained through mandible from A) cranial to B) caudal show bony erosion of bony cortex (arrow, B) without apparent evidence of bone marrow involvement.

From the Departments of Radiology (Yuh, Engelken, Dolan) and Dermatology (Whitaker), The University of Iowa College of Medicine, Iowa City, Iowa.

Reprints — William T. C. Yuh, MD, MSEE, Dept of Radiology, The University of Iowa Hospitals & Clinics, Iowa City, IA 52242.

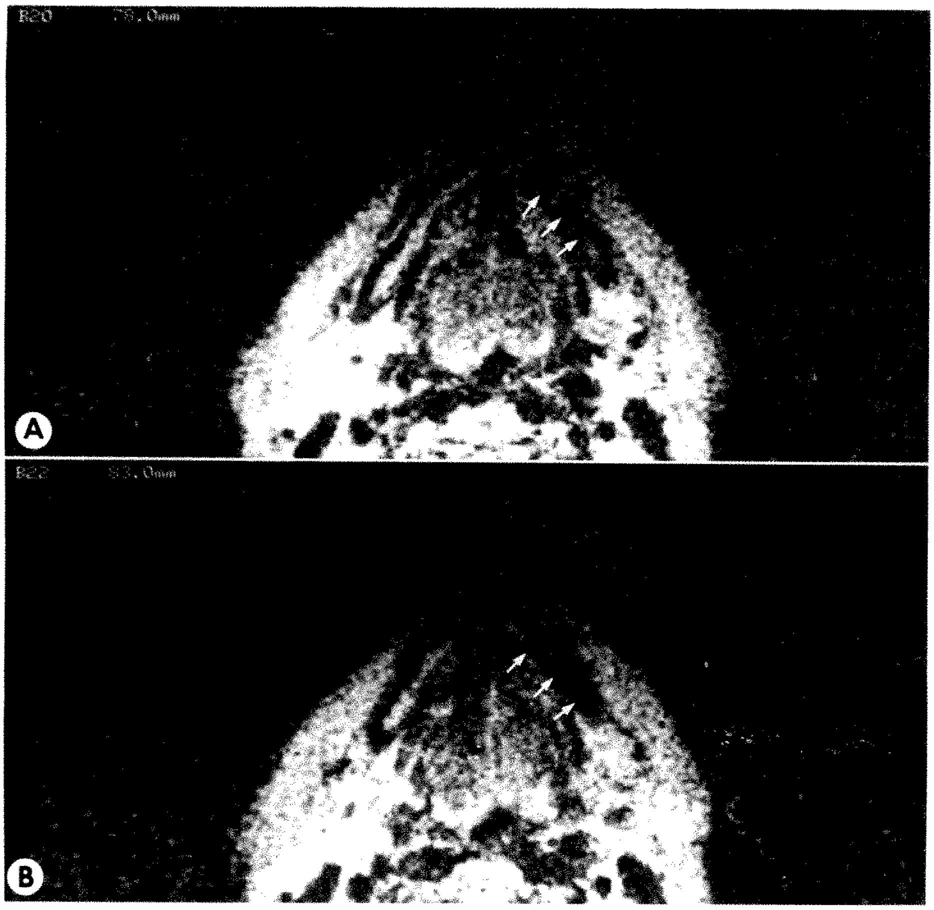

Fig 2. Axial T2-weighted images (TR 2,233, TE 80) closely corresponding to Fig 1A and B, respectively, show absence of normal bone marrow signal in left side of mandible (arrows) as compared with normal right side.

two thirds of the mandible that did not cross the midline and appeared to stop before the angle of the mandible. Tumor invasion of the bone marrow was demonstrated, but no lymph nodes were visibly enlarged.

The patient subsequently underwent a Mohs microscopically controlled procedure to obtain tumor-free peripheral soft tissue margins. There was direct tumor invasion of the bone, grossly seen as bone surface pitting and superficial erosion. A partial hemimandibulectomy was performed, and 61.2 Gy of radiotherapy were given.

Direct tumor invasion of the bone and neural spread of the carcinoma along the mental nerve and inferior alveolar nerve several centimeters into the ramus of the mandible were observed microscopically. Eighteen months after surgical excision and radiotherapy, the patient shows no signs of tumor recurrence.

DISCUSSION

Microcystic adnexal carcinoma is a rare, locally aggressive adnexal neoplasm initially described in 1982 by Goldstein et al.[1] Synonyms for this neoplasm in the literature include sclerosing sweat duct carcinoma, malignant syringoma, combined adnexal tumor of the skin, and sweat duct carcinoma with syringomatous features.[2]

Of the 33 literature cases of MAC, 29 have appeared on the face, with the lip being the most common site. Although it was originally described as occurring primarily in women, 17 of the cases occurred in women and 16 occurred in men. Ages ranged from 18 to 76 years with a mean of 47 years. Clinically, the lesions were described as yellow, erythematous or flesh-colored, firm, indurated plaques or nodules. The size of the tumors ranged from 1 to 9 cm with an average of 2 cm at the time of diagnosis. The tumors had been present for 1 month to 30 years before diagnosis.[2]

The locally aggressive and destructive nature of this neoplasm has been well documented. It has been shown to invade muscle, vascular adventitia, nerves, nerve sheaths, perichondrium, and periosteum.[3] Treatment has included local wide excision, irradiation alone, excision followed by irradiation, and the Mohs procedure. Cooper et al[4] reported that 9 of 15 patients had at least one recurrence after the initial surgical excision.

Microcystic adnexal carcinoma has a tendency to spread along nerves, and this spread has been a prominent feature in all cases. When it invades in this manner, passage into the skull and central nervous system is possible. It also has a propensity for extensive direct local invasion without clinically apparent symptoms. These findings indicate this neoplasm is much more aggressive than most cutaneous neoplasms. The neoplasm invaded deep tissue layers in every case, and muscle was involved in many of the cases.[2] Direct bone invasion, bone marrow replacement by tumor, and metastases have not been described previously. Bone has been resistant to most types of skin cancers. However, when bone invasion does occur, it is usually via a foramen or osseous suture line, or in an area of focal bone injury.[5]

The high incidence of recurrence may be secondary to the failure to recognize the tendency for aggressive and extensive invasion by these tumors without clinical radiographic evidence of tumor involvement. Thus, the surgical excision and/or irradiation treatment given to these patients may be inadequate. Tumor spread well beyond the clinically apparent lesion and invasion into the skull are thus important issues to assess. In our case, focal bone erosion secondary to direct tumor invasion was detected by CT scan; however, CT failed to detect the extensive bone marrow replacement by tumor.

Magnetic resonance imaging has been proven to be valuable in the detection of bone marrow disease. Although bony structure and perineural involvement was not obvious in our case, magnetic resonance imaging clearly demonstrated the abnormal bone marrow signal due to tumor infiltration preoperatively.

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TWENTY-SEVENTH POSTGRADUATE COURSE IN EAR SURGERY

The 27th Postgraduate Course in Ear Surgery will be held from April 26 to May 1, 1992, in Nijmegen, the Netherlands. For further information and registration form, please write to Prof Dr P. van den Broek, University Hospital Nijmegen, Department of Otorhinolaryngology, PO Box 9101, 6500 HB Nijmegen, the Netherlands; Fax: 80-540251.

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PATHOLOGY CONSULTATION

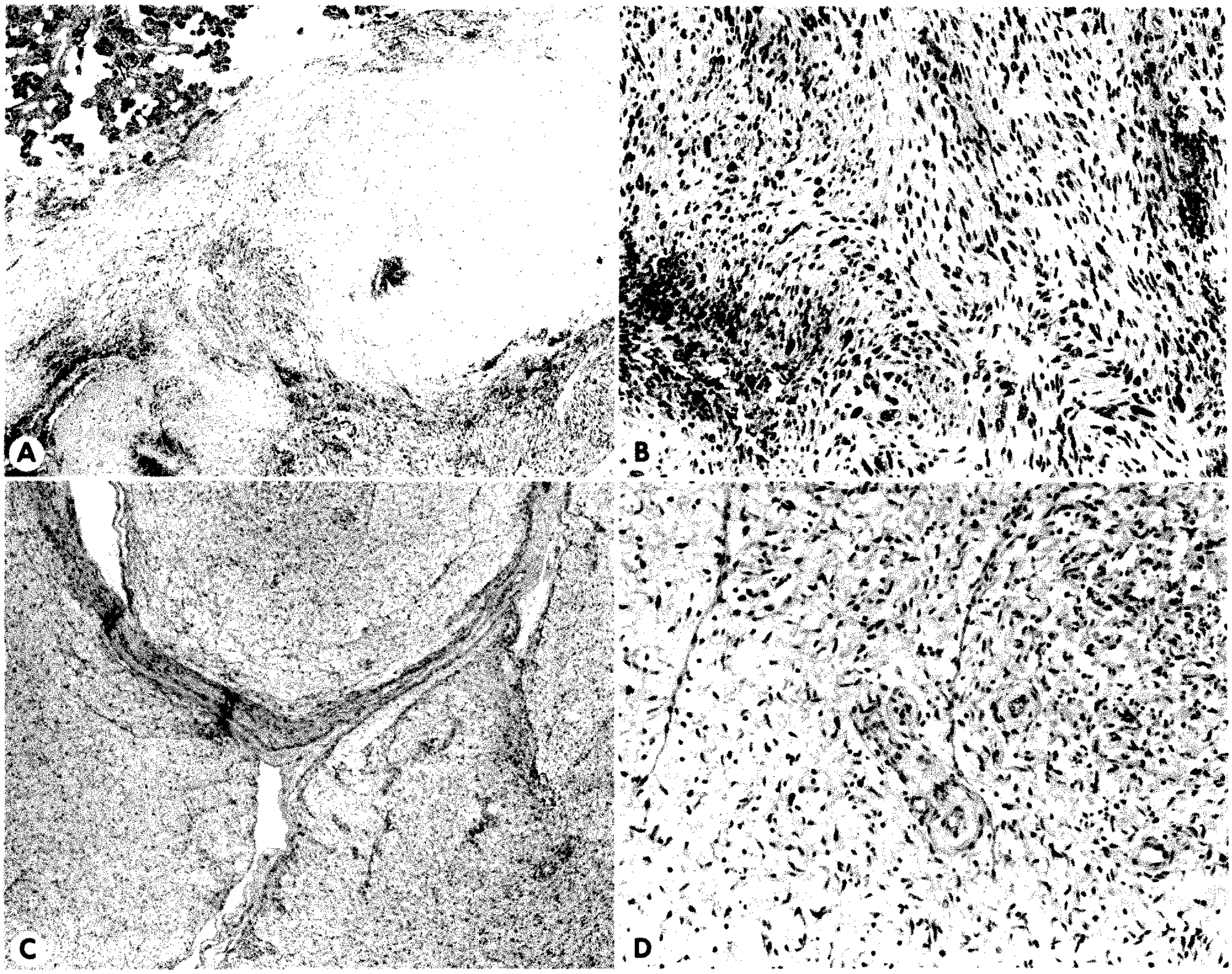
PRIMARY TUMORS OF THE FACIAL (EXTRACRANIAL) NERVE

NOUR SNEIGE, MD JOHN G. BATSAKIS, MD

HOUSTON, TEXAS

Nearly 25% of all primary neurogenous tumors arise from peripheral nerves in the head and neck. The extracranial parts of the facial nerve, however, rank low as potential sites. Their tumors nonetheless pose diagnostic and management problems. In the intraparotid location the neurogenous tumors most often present as mass lesions, accompanied, in one third of patients, by various degrees of facial weakness. With the exception of a peculiar predilection of childhood plexiform neurofibromas to afflict the facial nerve, the majority of the tumors are neurilemomas. Recurrences are unusual after surgical removal of either neurilemomas or neurofibromas. The rare facial nerve sarcoma is a high-grade malignancy.

Primary neoplasms of the seventh cranial (facial) nerve may be grouped according to their site of origin along the course of the nerve into intratemporal (temporal bone) and extracranial (parotid gland).[1-3] With rare exception, the neoplasms are derivatives of the Schwann cell and can arise anywhere from



Primary tumors of facial nerve. A) Intraparotid neurilemoma (H & E, original x40). Note thick capsule separating neoplasm (bottom left) from gland's parenchyma. B) Cellular area of neurilemoma in A (H & E, original x200). Note palisading to form Verocay bodies and foci of retrogressive change. C) Plexiform neurofibroma in 12-year-old girl (H & E, original x40). D) Higher magnification of neurofibroma in C (H & E, original x200).

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

ETIOLOGY OF FACIAL NERVE PARALYSIS

Etiologic Basis	*No. of Patients*
Bell's palsy	254
Trauma	122
Hemifacial spasm	101
Hunt's syndrome	67
Neonatal	50
Otitis media	31
Polyneuritis	7
Neoplastic disease	
Parotid gland neoplasm	6
Seventh nerve	5
Eighth nerve	5
Cerebral neoplasm	3
Leukemia	3
Others	3
Others	65
Total	722

Findings are those of facial nerve clinic at University of Tokyo as reported by Kobayashi.[10]

the glial–Schwann cell junction through the parotid to the muscles of facial expression. Of the approximately 150 reported examples, the great majority are histologically benign, with neurilemomas (see Figure; A,B) exceeding neurofibromas in a 10:1 ratio. Plexiform neurofibromas (see Figure; C,D), considered one of the stigmata of von Recklinghausen's disease, seem to have a predilection for occurrence in children.[4] Neurogenous sarcomas, usually high-grade, are rare.[1,5,6]

Most of the primary facial nerve tumors are found within the temporal bone, preponderantly in the tympanic part of the nerve, followed by the mastoid segment.[5] A third of the reported neoplasms (approximately 50 at this writing) are extracranial and intraparotid. In this location, the majority involve the main trunk of the nerve. With either a main-trunk or peripheral-branch origin the tumor may be multicentric.[1]

The frequency of occurrence of intraparotid facial nerve tumors is difficult to assess and is certainly biased by the experience of Janecka and Conley,[1] who reported 30 patients with primary neurogenous tumors of the facial nerve, 17 of whom had tumors of the extracranial parts of the nerve. Andrieu-Guitrancourt et al[7] estimate that facial nerve tumors make up 1% to 1.5% of "parotid region" tumors. Balle and Greisen[3] report an incidence of 1.4% (2 of 142) in parotidectomies. These estimates are considerably higher than the 0.25% and 0.14% reported by Eneroth[8] and Nussbaum et al,[9] who between them found only 3 in 1,502 parotid tumors.

Preoperative facial paralysis, with or without other otologic signs and symptoms, occurs in nearly 50% of patients with primary neurogenic tumors of the facial nerve.[1] It is considerably more frequent in patients with intratemporal neoplasms: 84% versus 35% extracranial in the series reported by Janecka and Conley.[1] The intraparotid tumors often present only as a parotid gland mass.

The higher percentage of preoperative facial paralysis in the intratemporal group of neoplasms as opposed to the intraparotid group is attributed to the nonyielding confinement of the nerve and its tumor in the temporal bone.[1]

The diagnosis of an intraparotid facial nerve neurogenic tumor is rarely made preoperatively. There is no characteristic symptom profile. The clinical course is usually one of a progressive facial weakness or growth of a mass. The latter finding is especially pertinent for the extracranial-intraparotid tumors, since a primary neurogenic tumor of the facial nerve is not the first consideration in the differential diagnosis of the causes for facial nerve paralysis (see Table[10]).

The only effective treatment for neurogenic tumors of the facial nerve is surgical removal, which can require sacrificing the nerve, followed by nerve grafting.[1,11,12] In any of the histologic forms identification of the nerve can be difficult, as nerve fibers are often splayed over the surface of the tumor. According to Bretlau et al,[11] this finding accounts for a persisting postoperative facial weakness or palsy in about half of the reported cases. Neurilemomas and neurofibromas (unassociated with von Recklinghausen's disease) are rarely recurrent. Neurogenous sarcomas, not unlike their counterparts elsewhere in the body, are high-grade malignancies with significant morbidity and mortality.[1]

The traumatic neuroma, much more common in the extracranial than the temporal part of the facial nerve, is the principal histopathologic differential diagnosis.[13,14] Rarely, a myoepithelioma or myoepithelial-dominant pleomorphic adenoma may show histopathologic fields closely resembling a neurilemoma.

A traumatic neuroma is a nonneoplastic and proliferative reparative response of the proximal part of the nerve to trauma or disruption. Its size is inversely related to the healing process in reestablishing the continuity of the nerve. The neuroma's appearance evolves with time. In its typical form it is composed of disrupted axons, Schwann cells, and a combination of endoneural and perineural fibroblasts in a collagenous matrix. With maturation there is a gradual loss of axons and an increase in collagenized stroma.

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The Seventh International Symposium on the Facial Nerve will take place June 9-14, 1992, in Cologne, Germany. For further information, please contact the Congress Secretary, Klinik und Poliklinik für HNO, Universität zu Köln, Kongressburo, Joseph-Stelzmann-Strasse 9, D-5000 Köln, Germany; 49-221-478-6190.

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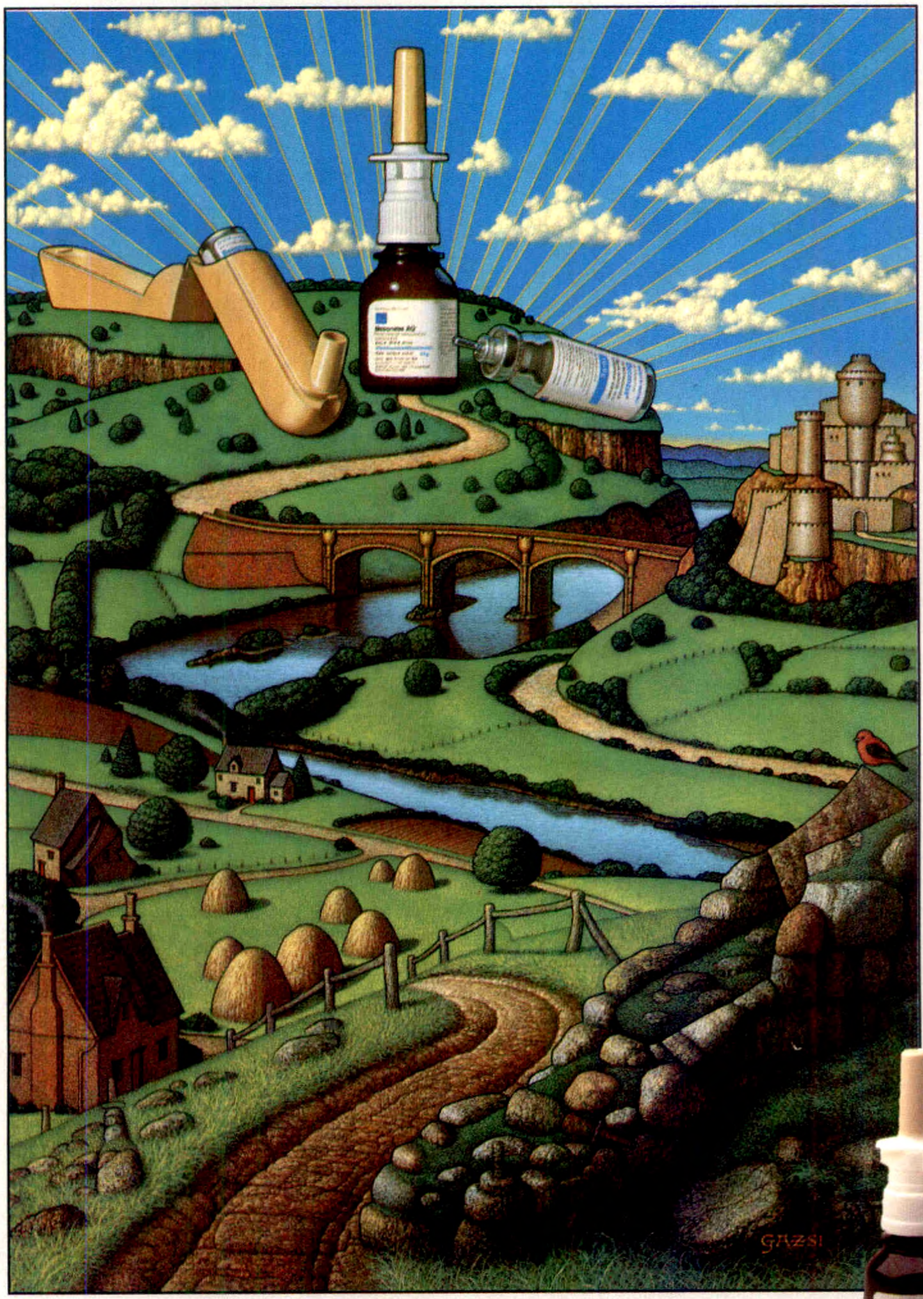

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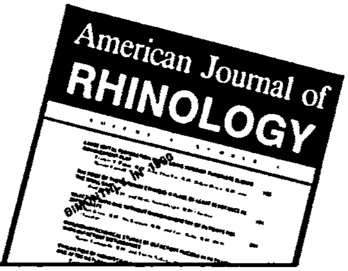

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STAPES SURGERY: COMPLICATIONS AND AIRWAY INFECTION

CHRISTIAN BRAHE PEDERSEN, MD
JENS ULRIK FELDING, MD
AARHUS, DENMARK

From a group of 1,111 patients who had stapedectomy or stapedotomy performed in a 10-year period, a thorough investigation was made of 11 patients who had a total hearing loss and 8 patients who developed a partial sensorineural hearing loss after operation. The data obtained indicate that postoperative infection with influenza virus may be responsible for unexpected complications following stapedectomy. A close relation was found between the appearance of complications and periods of epidemics of influenza.

KEY WORDS — complications, influenza, stapes surgery.

INTRODUCTION

For more than 30 years modern surgical treatment of otosclerosis has been able to improve hearing in a large number of patients all over the world. The surgical methods used for stapedectomy and stapedotomy have developed and improved. Most ear surgeons today prefer the small fenestra technique owing to the good hearing results (especially in the higher frequency area), stable hearing improvement, and few complications.[1-3] But the large fenestra technique has also shown excellent results in many ear surgeons' hands.[4,5]

The problem in stapes surgery today is to avoid such complications as partial sensorineural hearing losses or anacusis — complications that appear in approximately 1% of the operations in most published series.[6,7] In some cases of postoperative sensorineural hearing loss the factor responsible is known, eg, surgical trauma, granuloma, or development of a fistula in the oval window. In other cases postoperative complications develop for no obvious reason.[8] From a group of 1,111 patients who had stapedectomy or stapedotomy performed in a 10-year period we tried to evaluate the causes of sensorineural hearing loss in patients operated on for otosclerosis. A theory will be put forward indicating that infection with influenza virus in the postoperative period can be responsible for unexpected complications from stapedectomy. The theory is evaluated by illustrations of the coincidence in time of stapes surgery complications and epidemics of influenza.

MATERIAL

In the period 1976 to 1985, both years included, at the Otolaryngology Department of Aarhus University Hospital, a total of 1,111 stapedectomies were performed, and 1,091 ears were followed up for at least 1 year after the operation (98.2%). The average observation time was 2.4 years.

The diagnoses of the patients were otosclerosis in 97%, osteogenesis imperfecta in 1.4%, congenital stapes fixation in 1.2%, and traumatic stapedial fracture in 0.4%. Sixty-four percent of the patients were female and 36% were male. The average age was 44 years, with a range from 8 to 78.

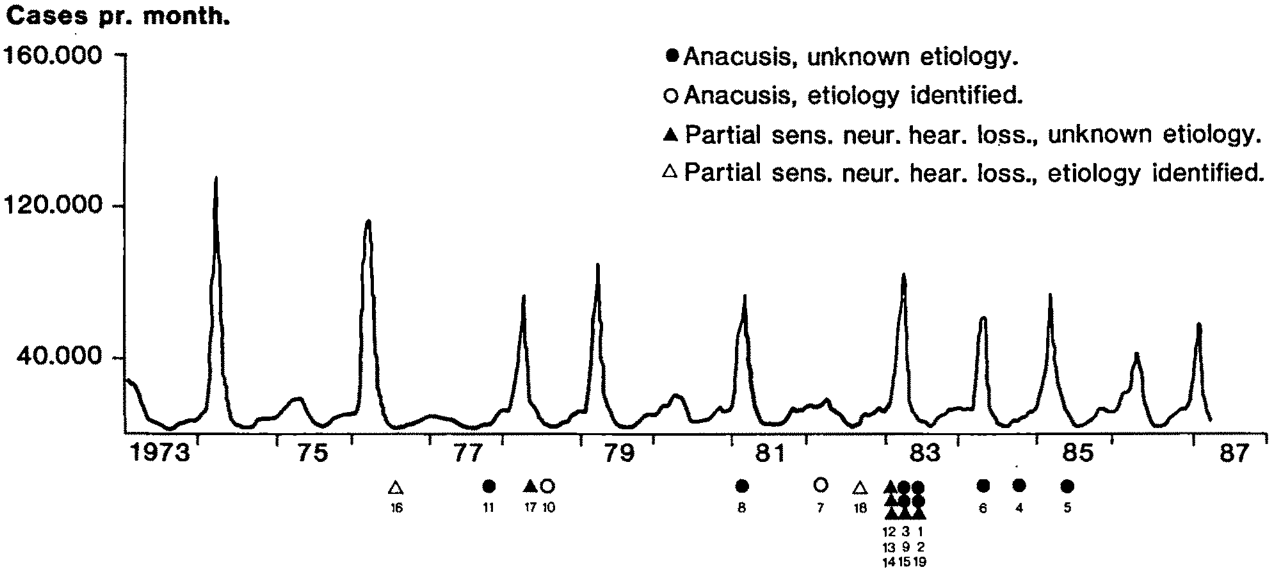
The large fenestra technique using the House prosthesis on vein was used during the first 5 years. In the last 5 years half of the patients were treated by the large fenestra technique and the other half were treated by the small fenestra technique using the Fisch prosthesis with a diameter of 0.4 mm.[9]

Eighty-eight percent of the ear operations were primary operations and 12% were revision operations. Of the 975 primary operations, the large fenestra technique was used in 699 cases and the small fenestra technique in 276. A total of 136 revision operations have been performed. The patients in this group came from the Otolaryngology Department of Aarhus University Hospital or from other otolaryngology departments in Denmark. The indication for reoperation was most often too large an air-bone gap. A few patients were operated on because of dizziness with suspicion of fistula. In the group of patients who had a revision operation performed, the primary operation most often was performed with a House or a Shea prosthesis. A small number of patients in their sixties were treated by stapes mobilization. At reoperation the Fisch prosthesis was used in 18 cases and the House prosthesis in 118.

All the operations were performed by two experienced ear surgeons. More than 99% of the operations were performed under local anesthesia after premedication. No antibiotic was routinely used. The patients normally stayed in the hospital for 2 days after the operation. Postoperative checkups were usually performed 3 weeks, 3 months, and 1 year after the operation. A number of patients continued audiologic control for some years and other patients were evaluated later when a new operation was performed on the other ear.

At the postoperative visits the patients were asked

From the Department of Otolaryngology, Aarhus University Hospital, Aarhus, Denmark.
REPRINTS — Christian Brahe Pedersen, MD, Dept of Otolaryngology, Aarhus University Hospital, DK-8000 Aarhus C, Denmark.



Incidence of influenza in Denmark 1973 through 1987, from Department of Epidemiology, Statens Seruminstitut, Copenhagen, Denmark (curve). Time relation between epidemics of influenza and development of total or partial sensorineural hearing loss following stapedectomy is shown.

if they were satisfied with their hearing and if dizziness or tinnitus was present. Audiometry and investigation of speech reception threshold (SRT) was performed. In cases of anacusis and sensorineural hearing loss the records were investigated in an attempt to clarify the reason for complications. Five of 11 dead ears were explored.

In this paper we focus on the development of sensorineural hearing loss. A partial sensorineural hearing loss is defined as a decrease in bone conduction of 20 dB or more at at least two frequencies between 500 and 4,000 Hz.

RESULTS

Of the 1,111 stapedectomies, 11 ears developed anacusis (1%) and in eight patients a partial sensorineural hearing loss was observed (0.7%). These patients were evaluated in detail to investigate the cause of the partial or total hearing loss.

In the group with partial sensorineural hearing loss, a reasonable explanation of the damage could be found in two patients. One patient was dizzy during the operation and another developed a fistula. In the other six patients no explanation of the partial sensorineural hearing loss was found.

In the group of 11 patients with dead ears a granuloma was found in 1 patient by exploration. In another patient with otosclerosis (three operations on the same ear) an incus was used to make a connection between the malleus and the oval window, but the incus dislocated into the vestibulum. In the last nine cases of anacusis no explanation of the anacusis was found.

One of the cases was special. The patient had a good hearing improvement after stapedotomy by the Fisch technique and was discharged from the hospital in good condition. She was readmitted to the hospital 8 days later with dizziness and anacusis in the operated ear. No exploration was performed. It was found that the entire family of the patient had influenza when the patient returned from the hospital. The patient had no fever, but she proposed spontaneously that her symptoms of influenza might have been masked by the dizziness.

To investigate whether airway infection could be responsible for other cases of side effects from stapes surgery, we used a diagram of epidemics of influenza in Denmark (see Figure, curve provided by P. Bjerregård). By plotting the time of all cases of anacusis and partial sensorineural hearing losses following stapedectomies on the diagram of influenza epidemics, we saw that there was an increase in side effects in the spring of 1983 during a large epidemic of influenza (see Figure). Fourteen of the 19 cases of hearing loss took place at the time of influenza epidemics. Four cases for which a reasonable explanation for the hearing loss could be identified are seen to be equally distributed through the observation period. A detailed report of the 19 cases is given in Tables 1 and 2. In most of the cases the anacusis or the partial sensorineural hearing loss developed shortly after the operation, but some late cases are also observed.

No serologic investigation to confirm infectious diseases has been performed, because an investigation of this type demands that serum from the patient before infection be available, and this was not the case.[10]

DISCUSSION

The complications in this sample of more than 1,100 stapedectomies are within a reasonable number. The incidence of anacusis at 1% corresponds to

TABLE 1. PATIENTS WITH ANACUSIS FOLLOWING STAPEDECTOMY

Pt No.	*Sex*	*Age*	*Reoperation*	*Type of Operation*	*Preoperative SRT*	*Hearing During and After Operation*	*Middle Ear Exploration*
1	F	69	+	H	40	U	–
2	F	22	–	H	45	G	–
3	M	34	–	H	35	G	+
4	M	58	+	F	85	(G)	+
5	F	63	–	H	85	G	–
6	F	31	–	F	30	G	–
7	F	58	+	I	50	G	+
8	F	31	–	H	25	G	–
9	F	47	–	H	45	G	+
10	M	22	–	H	30	G	+
11	M	68	–	H	85	G	–

Pt No.	*Time From Operation to Anacusis*	*Postoperative Tinnitus*	*Postoperative Dizziness*	*Cause Identified*	*Anacusis in Flu Epidemic*	*Operation on Opposite Ear*	*SRT Opposite Ear*
1	6 mo	(+)	(+)	–	+	–	10
2	2 wk	–	–	–	+	–	40
3	2 wk	+	–	–	+	B	15
4	10 d	–	–	–	–	–	75
5	7 y	–	–	–	+	A	20
6	8 d	–	–	–	+	–	20
7	5 d	(+)	(+)	Incus dislocation*	–	B	20
8	2 d	–	–	–	+	–	0
9	5 y	–	(+)	–	+	A	20
10	10 d	–	–	Granuloma	–	–	30
11	1 d	–	(+)	–	–	–	20

H — House (large fenestra) technique, F — Fisch (small fenestra) technique, SRT — speech reception threshold, U — unchanged, G — good, (G) — fairly good, (+) — slight, B — before, A — after.

*To vestibulum.

or is smaller than that presented in other, larger samples. Further, 0.7% of the patients had partial sensorineural hearing loss. Three of the eight patients with partial sensorineural hearing loss had an SRT of better than 40 dB hearing level on the operated ear. All patients with anacusis or partial sensorineural hearing loss had reasonably good hearing in the opposite ear.

Quite a large number of reoperations are present in this series. This is due to the fact that this department has a tradition of active stapes surgery, and more than 4,000 operations of this type were performed in the department earlier. Moreover, the department had a number of cases for revision operation from other otolaryngology departments. The material further is characterized by the participation of only two surgeons. In the first 5 years of the observation period only the large fenestra technique was used. In 1980 the small fenestra technique was introduced, and in recent years this technique has dominated the material.

With regard to the 11 cases of anacusis and 8 cases of partial sensorineural hearing loss, in only a few of these could an explanation for the perceptive hearing loss be established. It is characteristic that in 15 of the 19 patients a good hearing improvement was observed during the operation under local anesthesia.

Because of a case in which the patient had good hearing for some days postoperatively and thereafter developed anacusis, at the same time the whole family was sick with influenza, an evaluation of the relation between influenza epidemics and complications of stapes surgery was performed.

In Denmark the government-run Statens Seruminstitut performs an accurate registration of the incidence of a number of diseases, among them influenza. Owing to the small size of Denmark, epidemics of influenza will appear at the same time all over the country. Among the 15 patients for whom there could not be given a reasonable explanation of the sensorineural hearing loss, 13 of the sensorineural hearing losses developed during epidemics of influenza (see Figure). This finding makes it reasonable to believe that infection with influenza virus has played a role in the development of sensorineural hearing loss. In the cases in which the lesion did not develop in close relation to the operation, one can suggest that a route of infection via a fistula in the stapes region was present.

Even though it is reasonable to believe that infection with influenza virus is a dominating factor for

TABLE 2. PATIENTS WITH PARTIAL SENSORINEURAL HEARING LOSS FOLLOWING STAPEDECTOMY

Pt No.	*Sex*	*Age*	*Reoperation*	*Type of Operation*	*Preoperative SRT*	*Hearing After Operation*	*Time From Operation to Hearing Loss Identification*
12	M	40	–	H	45	G	2 wk
13	M	57	–	H	40	G	3 d
14	F	37	–	H	40	G	1 mo
15	M	56	+	H	65	U	3 mo
16	M	64	–	H	55	G	Perioperative
17	F	37	–	H	55	G	22 mo
18	F	67	+	H	65	U	1 wk
19	M	38	–	H	40	G	18 mo

Pt No.	*Postoperative SRT*	*Postoperative DL*	*Postoperative Tinnitus*	*Postoperative Dizziness*	*Cause Identified*	*Hearing Loss During Flu Epidemic*	*Operation on Opposite Ear*	*SRT Opposite Ear*
12	75	–	+	(+)	–	+	B	5
13	30	70	–	–	–	+	–	20
14	40	35	+	–	–	+	B	15
15	55	30	+	–	–	+	B	30
16	20	–	–	–	Operative trauma	–	–	20
17	35	–	–	–	–	+	A	40
18	85	55	–	–	Fistula	–	B	25
19	30	–	–	–	–	+	–	10

H — House (large fenestra) technique, SRT — speech reception threshold, G — good, U — unchanged, DL — discrimination loss, (+) — slight, B — before, A — after.

developing sensorineural hearing loss, especially in the nine cases in 1983, it cannot be proven that the hearing loss is caused by viral infection. As proof, a serologic measure of antibody before and after infection is necessary, and this was not possible.

That two experienced stapes surgeons within a few months should cause nine sensorineural hearing losses, when using the same operative technique, is unbelievable. It seems more likely that the lesion is due to factors in the surroundings. As a consequence of the observation that influenza virus might be an etiologic factor in unexplained cases of sensorineural hearing loss during stapes surgery, we stopped performing stapedectomy during epidemics of influenza, and in the years since, no sensorineural hearing loss after stapes surgery has been observed.

TABLE 3. NUMBER OF PATIENTS WITH TOTAL OR PARTIAL HEARING LOSS AFTER DIFFERENT TYPES OF OPERATION

	Primary Operation		*Revision Operation*	
	Large Fenestra	*Small Fenestra*	*Large Fenestra*	*Small Fenestra*
Anacusis	7/699	1/276	1/118	1/18
Partial sensorineural hearing loss	6/699	0/276	2/118	0/18

The small number of sensorineural hearing losses during the entire period makes it impossible to evaluate whether a large fenestra technique or a small fenestra technique is the safest. In the cases of sensorineural hearing loss a House prosthesis was used in 16 cases (89%), and in 2 cases a Fisch prosthesis was used (11%). The corresponding figures for the use of different prostheses in the whole sample were 74% and 26% (Table 3).

This new observation that a sensorineural hearing loss can develop during stapes surgery and infection with influenza virus is not going to serve as an excuse for bad results in stapes surgery, but can be an explanation for the ear surgeon who meets unexpected complications after a normally performed operation. Stapes surgeons should consider avoiding stapes surgery during epidemics of influenza, but as is also shown in this material, trouble might develop later in the postoperative period during influenza epidemics.

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NASOPHARYNGEAL FLORA IN THE FIRST THREE YEARS OF LIFE IN NORMAL AND OTITIS-PRONE CHILDREN

HOWARD FADEN, MD
LINDA BRODSKY, MD
MARY JANE WAZ, MD
JOHN STANIEVICH, MD
JOEL M. BERNSTEIN, MD
PEARAY L. OGRA, MD
BUFFALO, NEW YORK

Nasopharyngeal carriage of the three major middle ear pathogens (*Streptococcus pneumoniae*, nontypeable *Hemophilus influenzae*, and *Moraxella catarrhalis*) was evaluated prospectively in a group of 110 children followed up for the first 3 years of life. The findings suggested that nasopharyngeal carriage of middle ear pathogens increases significantly during respiratory illness among the general population of young children; however, otitis-prone children demonstrated a tendency to carry nontypeable *H influenzae* at an unusually high rate even during health. This propensity to carry nontypeable *H influenzae* might explain why nontypeable *H influenzae* is a major cause of recurrent or chronic otitis media.

KEY WORDS — *Hemophilus influenzae, Moraxella catarrhalis*, nasopharyngeal colonization, otitis media, *Streptococcus pneumoniae*.

INTRODUCTION

The normal flora of the nasopharynx is established early in life.[1] The bacterial composition of normal flora is relatively consistent among individuals.[2,3] For the most part, these bacteria are not pathogens in the upper airway; however, other, more pathogenic organisms such as *Streptococcus pneumoniae*, nontypeable *Hemophilus influenzae*, and *Moraxella catarrhalis* may also colonize the nasopharynx of healthy subjects.[2-9] Differences in carriage rates of potentially pathogenic bacteria may predispose children to the increased risk of developing recurrent respiratory disorders such as otitis media.

The present study was designed to characterize nasopharyngeal carriage patterns of middle ear pathogens among children followed up prospectively for 3 years. The impact of intercurrent respiratory illness on colonization was assessed. In addition, the nasopharyngeal floras of normal and otitis-prone (OP) children were compared to determine whether differences in colonization patterns with specific bacteria, ie, nontypeable *H influenzae*, might account for recurrent middle ear disease.

METHODS AND MATERIALS

General Design. Children were enrolled into a prospective study of the natural history and immunology of otitis media. The participants were examined four times each year at regularly scheduled visits and during episodes of respiratory illness. At each visit, the children's ears were examined with pneumatic otoscopy and tympanometry by one of the authors (H.F.). The presence of otitis media, as well as other respiratory illnesses, was noted. Nasopharyngeal cultures were obtained at each visit and the bacterial flora was identified.

Population. Male, female, white, black, and Spanish-American children less than 2 years of age were enrolled into the study through advertisement over the radio, on the television, in newspapers, and from correspondence with every pediatrician in the community, from January 1986 through December 1989. Children with known immunologic disorders or congenital anomalies, especially those involving the respiratory tract, were excluded from the study. Informed consent was obtained from the parents at the time of entrance into the study. Information concerning infant feeding, parental smoking, allergies, otitis media, and day-care enrollment were solicited. The children were routinely examined every 3 months with pneumatic otoscopy and tympanometry. Children were also examined at times of respiratory illness. Nasopharyngeal culture specimens were obtained at each visit after determining that antibiotics had not been administered within the previous 3 weeks.

Nasopharyngeal Cultures. Specimens from the nasopharynx were obtained with calcium alginate swabs. The swabs were transported to the bacteriology laboratory in brain-heart infusion (BHI) broth. The specimens were cultured on trypticase soy agar with 5% sheep blood, chocolate agar, phenylethanol agar, and MacConkey agar, and in BHI broth (Remmel, Lenexa, Kansas). The plates were incubated at 37°C in 5% carbon dioxide with the exception of the MacConkey plate and the BHI broth, which were incubated in a non–carbon dioxide environment. Bacterial isolates were identified by standard laboratory techniques.[10] Although growth of all aerobic bacteria was recorded, only the data from the three major middle ear pathogens were analyzed for this report. *Streptococcus pneumoniae*

From the Division of Infectious Diseases (Faden, Ogra) and the Departments of Pediatrics (all authors) and Otolaryngology (Bernstein, Brodsky, Stanievich), State University of New York School of Medicine at Buffalo, and Children's Hospital of Buffalo (all authors), Buffalo, New York. The work was supported in part by National Institutes of Health/National Institute of Child Health and Human Development grant HD 19679.

REPRINTS — Howard Faden, MD, Division of Infectious Diseases, Children's Hospital of Buffalo, 219 Bryant St, Buffalo, NY 14222.

TABLE 1. RECOVERY OF MIDDLE EAR PATHOGENS IN NASOPHARYNX ACCORDING TO AGE

Age (mo)	*No. of Cultures*	*No. of Pathogenic Species**			
		0	*1*	*2*	*3*
2-12	84	45	32	19	4
13-24	135	34	35	22	9
25-36	84	43	34	19	4

**Streptococcus pneumoniae*, nontypeable *Hemophilus influenzae*, and *Moraxella catarrhalis*. Data represent percentages of cultures.

TABLE 2. RECOVERY OF SPECIFIC MIDDLE EAR PATHOGENS IN NASOPHARYNX ACCORDING TO AGE

Age (mo)	Streptococcus pneumoniae	*Nontypeable* Hemophilus influenzae	Moraxella catarrhalis
2-12	21	25	30
13-24	34	34	37
25-36	36	29	24

Data represent percentages of cultures.

was identified by bile solubility. Nontypeable *H influenzae* was characterized by X and V factors and by the absence of agglutination with typing sera. *Moraxella catarrhalis* was identified by the oxidase reaction, Gram stain, and Quad Ferm (Api, Analytab Products, Plainview, NY).

Statistical Analysis. Nasal carriage rates of nontypeable *H influenzae*, *S pneumoniae*, and *M catarrhalis* were determined and correlated to age and health status. The children were subdivided into non–otitis prone (NOP) and OP groups. Otitis-proneness was defined as four or more episodes of otitis media in the first year of life, or six or more episodes in the first 2 years of life, or the need for tympanostomy tubes in the first 2 years of life. Tympanostomy tubes were placed for either fluid persisting for more than 3 months or recurrent otitis media exceeding six episodes. In order to be evaluated, children must have had one or fewer episodes of otitis media at the time of entry into the study, been followed up for more than 1 year, and had three or more nasopharyngeal cultures in the first 2 years of life. Comparisons of carriage rates between groups were analyzed by χ^2 and the Fisher exact test.

RESULTS

Population. One hundred ten children were enrolled in the study. Sixty were boys and 50 were girls. They ranged in age from 2 months to 36 months during the period of observation. Fifteen percent of the study population were enrolled in day-care.

Visits and Nasopharyngeal Cultures. There were 303 visits. One hundred thirty represented healthy visits and 173 represented ill visits. Eighty-nine of the ill visits were for otitis media and 84 were for other upper respiratory tract illnesses. Specimens for nasopharyngeal cultures were taken at every visit.

Recovery of Middle Ear Pathogens From Nasopharyngeal Cultures. Sixty percent of the total cultures taken yielded one or more pathogens. Table 1 compares the proportion of cultures that yielded none to three pathogens in each of the first 3 years of life. The numbers of different pathogenic species recovered from the nasopharynx were similar in each of the first 3 years of life. Approximately 40% of the cultures contained no identifiable pathogen. Nearly one third of the cultures yielded a single pathogen, while less than one fourth had two or three pathogens. Table 2 illustrates the frequency with which specific pathogens were recovered. *Streptococcus pneumoniae*, nontypeable *H influenzae*, and *M catarrhalis* were each recovered in approximately 21% to 37% of the cultures in the first 3 years of life. Group A *Streptococcus* was recovered in 4% and 6% of the cultures in the second and third years of life, respectively, but was not isolated in the first year. *Hemophilus influenzae* type b was not recovered in any of the nasopharyngeal cultures.

The recovery of middle ear pathogens was next compared during healthy and ill periods. Upper respiratory tract infection and otitis media were combined and analyzed as a single group. Since the aforementioned results did not demonstrate a significant effect of age in the first 3 years of life on the recovery of middle ear pathogens in the nasopharynx, the results from each of the years in the present analysis were pooled. Figure 1 compares the number of different pathogens recovered during healthy and ill visits. The recovery of pathogens was significantly more frequent during illness than health ($p < .001$). Each of the middle ear pathogens was recovered significantly more often during illness (Fig 2).

In order to determine whether carriage of specific middle ear pathogens was a risk factor in the development of recurrent otitis media, nasopharyngeal colonization rates were compared between a group of 17 OP children and a group of 17 NOP children during health and illness. All of the NOP children had fewer than three episodes of otitis media by 2 years of age, and 5 had no episodes. Among the OP

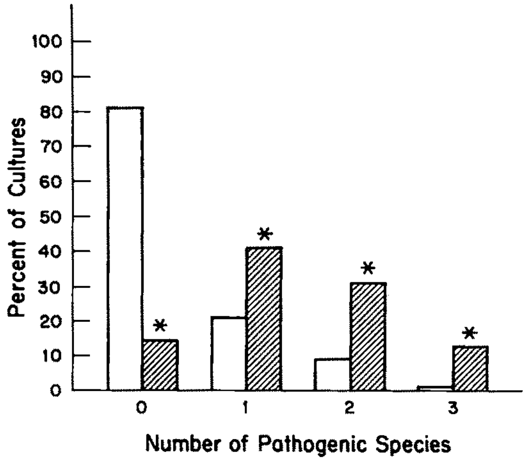

Fig 1. Comparison of nasopharyngeal carriage of middle ear pathogens during health (open bars) and illness (shaded bars). * — $p < .001$.

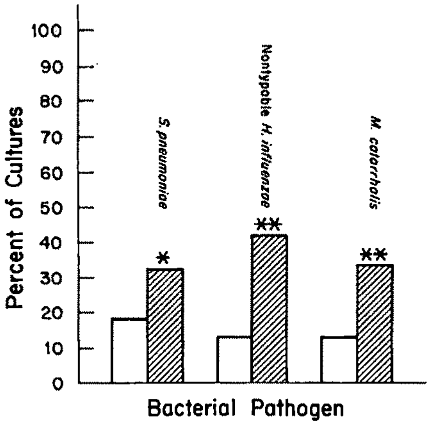

Fig 2. Comparison of nasopharyngeal carriage of *Streptococcus pneumoniae*, nontypeable *Hemophilus influenzae*, and *Moraxella catarrhalis* during health (open bars) and illness (shaded bars). * — $p<.05$, ** — $p<.001$.

TABLE 3. COMPARISON OF DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF NON-OTITIS-PRONE AND OTITIS-PRONE CHILDREN

Characteristics	*Non-Otitis-Prone*	*Otitis-Prone*	*p*
No. of subjects	17	17	NS
Male (No. of children)	13	10	NS
Race (white:black:other)	17:0:0	16:1:0	NS
Breast-fed (No. of children)	13	10	NS
Day-care (No. of children)	0	2	NS
No. of healthy visits	40	42	NS
No. of ill visits	60	70	NS
No. of visits with URI alone/No. with OM	39/21	10/60	<.001
Parental history (No. of children)			
Allergic	11	8	NS
Smoker	8	9	NS
Otitis-prone	11	13	NS

URI — upper respiratory tract infection, OM — otitis media, NS — not significant.

children, 5 had placement of tympanostomy tubes in the first year of life, and 10 had tympanostomy tubes in the second year; 80% of the tubes were placed for persistence of middle ear effusion beyond 3 months, and 20% of the tubes were placed for recurrent otitis media beyond six episodes. The demographic and clinical characteristics of the children are compared in Table 3. The two groups were similar in most respects except for the proportion of visits that were due to upper respiratory tract infections alone versus otitis media; during respiratory illnesses, the OP group had otitis media more often than the NOP group. A total of 82 cultures were taken during healthy visits: 40 from NOP children and 42 from OP children. Another 130 cultures were taken during ill visits: 60 from NOP children and 70 from OP children. Figure 3 illustrates the comparative recovery rates of the three major middle ear pathogens. Otitis-prone children carried middle ear pathogens more often than NOP children when they were healthy (Fig 3A). In particular, nontypeable *H influenzae* was carried almost seven times as frequently in OP children as in NOP children ($p<.01$). During respiratory illnesses, OP children carried each of the pathogens significantly more often ($p<.01$). As in health, nontypeable *H influenzae* was carried most often in illness in the OP group.

DISCUSSION

The present study suggests that nasopharyngeal carriage of major ear pathogens is relatively common in the first 3 years of life. Approximately 60% of cultures yielded one or more pathogens. A very similar experience has been noted in Sweden.[2] Each of the pathogens, *S pneumoniae*, nontypeable *H influenzae*, and *M catarrhalis*, was recovered from 20% to 40% of the specimens during the period of observation. Carriage rates for these pathogens differ slightly among studies. For example, carriage of *S pneumoniae* in children less than 3 years of age was reported previously to range between 21% and 50%.[2,5] Overall, carriage of nontypeable *H influenzae* in young children has been reported to be between 10% and 32%.[2,7] Variables that may account for differences in carriage rates include the presence of an active respiratory illness.[7,11,12] As noted in the present study, others[7,8] have observed a direct effect of respiratory illness on carriage of respiratory pathogens: the more recent the illness, the greater the impact on carriage. The present report demonstrated a fivefold increase in colonization rate of

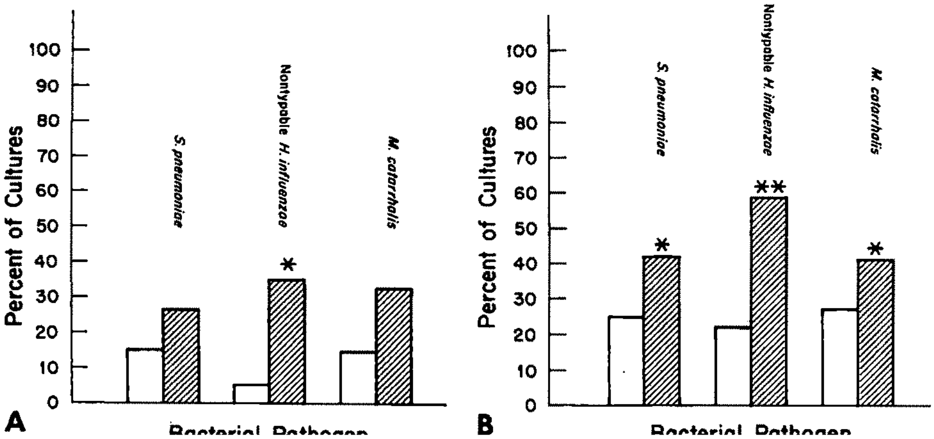

Fig 3. Comparisons of nasopharyngeal carriage of *Streptococcus pneumoniae*, nontypeable *Hemophilus influenzae*, and *Moraxella catarrhalis* in non-otitis-prone (open bars) and otitis-prone (shaded bars) children. A) During health. * — $p<.01$. B) During illness. * — $p<.05$, ** — $p<.001$.

middle ear pathogens during illness. In addition, the number of different pathogens carried increased significantly. In an earlier report from our laboratory, the rise in carriage rate of pathogens during episodes of otitis media was accompanied by an increase in the density of bacterial pathogens in the nasopharynx and a concurrent decline in nonpathogenic flora such as *Streptococcus viridans*.[13] Nontypeable *H influenzae* exhibited the highest carriage rate among pathogens during illness (42%). Sϕrensen et al[14] studied a slightly older group of children, 4 to 6 years old, during episodes of serous otitis media and found increased carriage of *S pneumoniae*. The relative infrequency of group A streptococcal carriage and the total absence of *H influenzae* type b carriage in the first 3 years of life in the present study may explain the minor role of these pathogens in the production of otitis media of early childhood.[15]

One of the more provocative aspects of the present investigation was the observation that OP children were more frequently colonized with middle ear pathogens than a comparable group of NOP children. Increased colonization rates were noted for each of the pathogens during illness. Prellner et al[11] only observed increased colonization with *M catarrhalis* among OP children during episodes of acute otitis media. Their study did not document any differences in carriage rates between the two groups during health.[11] In a preliminary report from a second group of investigators in Sweden, OP children were colonized more often with nontypeable *H influenzae* than NOP children during illness as well as during health.[16] In the present study a significantly higher colonization rate with nontypeable *H influenzae* was observed among OP children compared to NOP children during healthy periods. The first Swedish study took place among children enrolled in a day-care program, while only 15% of subjects in the present study were in day-care. It is possible that day-care experience may affect carriage rates and result in a more uniform distribution of pathogens among subjects.[6,11,12] The higher rate of carriage of pathogens (80%) among children during healthy periods in the first Swedish study, contrasted with 30% in the present study, would tend to support this argument.

In summary, the flora in the upper airway undergoes changes during episodes of respiratory illness. Bacteria with the potential to produce local disease such as otitis media or sinusitis become more common. Children who are prone to recurrent ear infections appear to carry middle ear pathogens more frequently than normal children. The reason for increased carriage is unclear and must await additional studies that focus on host factors and yet-undefined environmental factors.

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CHLAMYDIA TRACHOMATIS IN THE ETIOLOGY OF ACUTE OTITIS MEDIA

PETER CY WEBER, MD
PITTSBURGH, PENNSYLVANIA

PETER J. KOLTAI, MD
ALBANY, NEW YORK

In an effort to show that *Chlamydia trachomatis* (CT) may be involved in the causation of acute otitis media (AOM), we performed three experiments. In the first, we inoculated the tympanic bullae of 6 chinchillas with CT. Five of the 6 inoculated animals developed CT AOM. In the second experiment, we sprayed the nasopharynx of 10 chinchillas with CT. Of these, 8 developed both pharyngitis and AOM, and in 6, live CT was cultured from the middle ear and pharynx. In the third experiment, 5 chinchillas had their conjunctiva inoculated with CT. Three developed CT conjunctivitis. Of these, 2 developed CT pharyngitis and 1 developed CT AOM. We concluded that CT will cause AOM in the chinchilla by direct inoculation into the middle ear as well as indirectly by infection of the nasopharynx and conjunctiva.

KEY WORDS — acute otitis media, *Chlamydia trachomatis*, conjunctivitis, pharyngitis, upper respiratory tract infection.

INTRODUCTION

The etiology of acute otitis media (AOM) in children has been extensively studied.[1-9] In 70% to 80% of the cases a specific bacterial or viral agent can be identified. The most common are *Hemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis.* In 20% to 30% of patients with AOM no organisms can be isolated. Various reasons may explain this; however, the possibility that some of these cases may be due to organisms previously not suspected of causing AOM needs to be investigated.

Chlamydia trachomatis (CT), an intracellular parasite with some resemblance to gram-negative bacteria, is a causative agent in some cases of upper respiratory tract infections and conjunctivitis in infants and children.[10,11] Since the middle ear is a mucosal lined cavity in continuity with the upper respiratory tract, it seems plausible that CT may find the middle ear a suitable environment for reproduction, resulting in AOM. A causal link between childhood upper respiratory tract infections and conjunctivitis due to CT and subsequently leading to AOM has been previously proposed.[10-15] Banks et al[11] recovered CT in two thirds of chronic serous otitis media cases by using positive direct fluorescence antibody tests. Chang et al[12] found CT as the etiologic agent in 2 of 12 cases of AOM. Of interest, San Joaquin et al[15] failed to culture CT in the middle ear fluid in 164 children with upper respiratory tract infections and AOM. Dawson et al[13] also had difficulty isolating CT in children with AOM, finding it in only 2 of 137 children tested. These conflicting clinical studies provide equivocal data; thus, the question of CT's role in AOM remains unanswered.

The chinchilla is a well-recognized animal model for the study of the pathogenesis and treatment of AOM.[16,17] We performed three experiments in an effort to demonstrate that CT may be a factor in the pathogenesis of AOM.

MATERIALS AND METHODS

Chlamydia Inoculum. Positive CT specimens from hospital patients were pooled together in chlamydia minimal essential medium (CMEM), which consists of streptomycin sulfate, vancomycin hydrochloride, and nystatin in 10% fructose-buffered saline. Dram vials containing a monolayer of McCoy cells were inoculated with 0.2 mL of the pooled specimens. The drams were centrifuged at 2,000 rpm for 1 hour in a Sorvall GLG-2B centrifuge, after which the inoculum was pipetted off. One milliliter of CMEM was introduced into the dram vials, along with 0.02 mL of 10% cytochalasin B. The drams were incubated at 35°C for 48 hours, after which the coverslips were scraped and the solution was pipetted off and pooled together in a large test tube. The solution was diluted at a 1:1 ratio with 2-sucrose-phosphate solution. The resultant mixture was divided into 0.5-mL aliquots and stored in Provial-1 containers at −70°C for 2 hours before being stored indefinitely in liquid nitrogen.

The aliquots, when needed, were quick-thawed and the above process, starting with the inoculation step, was repeated, halting just before the addition of 2-sucrose-phosphate solution. The solution, pooled into one large tube, was slowly centrifuged at 200g for 10 minutes to remove cellular debris. The supernatant was centrifuged at 20,000g for 1 hour at 4°C to pellet the elementary bodies. The pellet was resuspended with CMEM at one tenth

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From the Section of Pediatric Otolaryngology, Department of Surgery, Albany Medical College, Albany, New York. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Albany Medical College.

REPRINTS — Peter Cy Weber, MD, Dept of Otolaryngology, University of Pittsburgh, Pittsburgh, PA 15221.

the original volume. The solution was divided into 1-mL aliquots and stored at −70°C in Provials until needed.[18]

Before use the aliquots were quick-thawed and titrated in McCoy cells as previously described. Serial tenfold dilutions of 0.1 mL of the inoculum were diluted with 2-sucrose-phosphate solution, and the inoculum was judged effective only if inclusion bodies were identifiable at $>10^4$ dilution.

Chlamydia Cultures. The middle ear, pharyngeal, and conjunctival specimens were transported in 1 mL of CMEM, whereupon 0.2 mL of this solution was used to inoculate the monolayer of McCoy cells in the dram vials. The same culture process as previously described was employed. The McCoy cells were scraped, aspirated, placed on slides, and prepared by a standard monoclonal CT culture confirmation test (Syva/Microtrak) to be examined for inclusion bodies under the fluorescent microscope. Each specimen was also cultured for aerobic (blood and chocolate agar plates) and anaerobic growth.

Experiment 1. The right tympanic bullae of six chinchillas were surgically prepared and had 0.3 mL of a standard CT inoculum injected via a 25-gauge needle. As a control, the tympanic bullae of six chinchillas were inoculated with 0.3 mL of normal saline. The inoculations were done in a blinded fashion so that the surgeon did not know whether he was injecting CT inoculum or normal saline. All animals were then observed daily for the development of AOM, defined as a red or dull bulging tympanic membrane with decreased tympanic membrane movement to pneumatoscopy. When a chinchilla was determined to have signs of AOM the ear canal was cleansed with alcohol, a myringotomy was performed, and the middle ear fluid was suctioned sterilely into a Senturia trap. The aspirates were then cultured as previously described.

At the end of the experiment, all remaining chinchillas that showed no signs of AOM underwent tympanocentesis with aspirates cultured as described.

Experiment 2. We sprayed the nasopharynx of 10 chinchillas with 0.3 mL of CT inoculum. As a control we sprayed the nasopharynx of 5 chinchillas with 0.3 mL of normal saline. Again the investigator was not aware whether he was spraying normal saline or CT inoculum. The animals were observed daily for the development of both AOM and pharyngitis, evidenced by oropharyngeal erythema and rhinorrhea. Each chinchilla that showed evidence of AOM underwent aspiration and culture as described in experiment 1. Each animal that showed signs of pharyngitis or AOM also had a throat swab that was cultured for CT, aerobes, and anaerobes.

At the end of the experiment all remaining chinchillas underwent throat swabs and middle ear aspirations with the appropriate cultures.

Experiment 3. In the third experiment, five chinchillas had their right conjunctiva sprayed with 0.3 mL of CT inoculum and five control chinchillas had 0.3 mL of sterile saline sprayed into their conjunctiva. The investigator was again blinded to this part of the experiment. The chinchillas were checked daily for signs of conjunctivitis, pharyngitis, and AOM. If any chinchilla exhibited the signs of infection previously described, appropriate cultures were obtained in the manner already discussed.

At the end of the experiment all remaining chinchillas underwent conjunctival swabs, throat swabs, and middle ear aspiration with appropriate cultures.

For all surgical procedures, the chinchillas were anesthesized with 40 mg/kg of a 10% ketamine hydrochloride solution injected intramuscularly.

RESULTS

Experiment 1. Five chinchillas out of six that had their tympanic bullae inoculated with CT developed signs of AOM. The middle ear aspirates of all five chinchillas were culture-positive for CT as interpreted by our bacteriology laboratory. No other bacterial pathogens were cultured from these middle ear aspirates. In the one chinchilla inoculated with CT that had no signs of AOM, the middle ear aspirate was culture-negative for CT and other pathogens.

Two of the six chinchillas that had sterile saline injected into their tympanic bullae developed signs of AOM. The middle ear aspirates for these two were culture-negative for CT and bacterial pathogens. The remaining four controls were also culture-negative for CT and bacterial pathogens.

All infections were identified within 14 days and the experiment was terminated after 30 days.

Experiment 2. Eight chinchillas out of 10 that had CT sprayed into their nasopharynx developed signs of AOM and pharyngitis. Middle ear aspirates and throat cultures from 6 of these chinchillas were culture-positive for CT, while those from the other 2 were not. All 8 middle ear aspirates were negative for other bacterial pathogens. Throat cultures from the 10 chinchillas inoculated with CT were negative for bacterial pathogens, although they all were positive for staphylococci and 7 also exhibited Enterobacteriaceae. None of the 5 control animals developed pharyngitis or AOM, and throat cultures only showed staphylococci and Enterobacteriaceae.

All infections were noted in 17 days and the experiment was terminated after 30 days.

Experiment 3. Three chinchillas out of five that had CT sprayed into their conjunctiva developed conjunctivitis, and all three were culture-positive for CT on eye cultures. Two of these three chinchillas also developed pharyngitis, which was CT culture-positive, and one developed AOM, which was CT culture-positive. Of these five chinchillas, three grew staphylococci from eye cultures, and four from throat cultures. None of the five control chinchillas developed conjunctivitis, pharyngitis, or AOM. Cultures were negative for pathogens, although eye swabs did grow staphylococci, as did throat swabs.

All infections were identified within 16 days and the experiment was terminated after 30 days.

DISCUSSION

Chlamydia trachomatis will cause AOM in the chinchilla when the organism is actively inoculated into the ear, nasopharynx, or eye. The first experiment showed that CT is able to proliferate in the middle ear and cause AOM. This is not unexpected, since CT, an intracellular organism, grows best on columnar epithelium, with which the middle ear is lined.[10,12] Indeed, the middle ear appears to be a hospitable environment for the growth of CT. The presumed cause of AOM in the two control chinchillas was trauma from the transbullar injection, since no pathogens were identified with culture.

The second experiment showed that CT can proliferate in the columnar epithelium of the nasopharynx, causing pharyngitis as well as traversing the eustachian tube and causing AOM. Our results are consistent with the observations of Banks et al,[11] who found a clinical correlation between CT pharyngitis and AOM in children. Moreover, the results are consistent with the accepted model of the relationship between pharyngitis and AOM, with the same pathogens involving the nasopharynx and the middle ear.[3,5,6]

The third experiment showed that CT inoculated into the eye will cause conjunctivitis and that this can subsequently lead to CT pharyngitis and AOM. The likely route of infection from the eye to the nasopharynx is via the nasolacrimal duct, and from there it can spread to the middle ear via the eustachian tube.

These findings perhaps clarify the controversy surrounding the studies that have suggested that CT may be an etiologic agent in AOM and serous otitis media.[10-15,19] Rettig[14] has pointed out that Banks et al[11] did not confirm positive CT fluorescent antibody test results with cultures, and that in a study by Shehab et al[19] four of the nine children positive for CT were also infected with known respiratory pathogens. Chang et al[12] found CT in 16% of patients with AOM, but they felt they had not tested enough subjects for significant results. Dawson et al[13] and San Joaquin et al[15] found CT difficult to culture because of pretreatment with a variety of antibiotics.

If the chinchilla is an accurate model of the pathogenesis of otitis media in humans, our results suggest that CT may be a cause of AOM in infants and children, especially those with CT pharyngitis and CT conjunctivitis. These findings may account for some of the 20% to 30% of children with AOM in whom no specific bacterial or viral agent can be identified.[20] The difficulty in demonstrating the incidence of AOM secondary to CT in clinical studies among children has been reviewed. While positive cultures remain the gold standard of proof in linking an organism and a disease, perhaps measuring CT serum immunoglobulin G antibodies may be of benefit, on the basis of the observation that bacterial antibodies for *S pneumoniae* and *H influenzae* rise in response to AOM.[21-24]

In conclusion, we have shown that CT will cause AOM in the chinchilla by direct inoculation into the middle ear, as well as by indirect infection of the nasopharynx and conjunctiva. This finding suggests that the previously proposed etiologic link between CT and upper respiratory tract infections resulting in AOM may have scientific validity.

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FAMILIAL SENSORINEURAL HEARING LOSS: A CORRELATIVE STUDY OF AUDIOLOGIC, RADIOGRAPHIC, AND VESTIBULAR FINDINGS

KENNY H. CHAN, MD
ELIZABETH A. EELKEMA, MD
JOSEPH M. R. FURMAN, MD, PHD
DONALD B. KAMERER, MD
PITTSBURGH, PENNSYLVANIA

A multidisciplinary approach to the study of a family with autosomal dominant sensorineural hearing loss is presented. The affected family members underwent extensive clinical and laboratory evaluation. They were found to have various degrees of bilateral congenital inner ear anomalies as imaged by computed tomography. The degree of structural abnormalities in the inner ears correlated with the severity of hearing impairment. Vestibular testing revealed nonspecific abnormalities generally correlating with audiologic and radiographic findings. This report presents a unique form of sensorineural hearing loss not previously described and is the first in-depth clinical study of nonsyndromal "Mondini dysplasia" occurring in a family.

KEY WORDS — autosomal dominant inheritance, Mondini dysplasia, sensorineural hearing loss.

INTRODUCTION

It is estimated that between 2,000 and 4,000 profoundly deaf infants are born in the United States every year.[1] Approximately 35% to 50% of the cases of profound childhood deafness are classified as genetic. The majority of genetic hearing loss is not associated with other anomalies or syndromes. According to Konigsmark and Gorlin[2] there are at least 16 types of hereditary hearing loss with no associated abnormalities. These various types can be separated by mode of transmission, age at onset, severity of hearing loss, and type of audiogram. Several studies[3,4] have shown that a high percentage of cases (about 40%) are autosomal recessive in origin. Autosomal dominant sensorineural hearing loss (SNHL) accounts for only approximately 10% of reported cases.

Autosomal dominant SNHL can be further classified clinically into the following subtypes: severe, progressive early-onset, unilateral, low frequency, middle frequency, and high frequency.[2] Documentation of these dominant SNHL types included audiologic, radiographic, histologic, and vestibular assessments. Other than audiologic data, the studies were generally partial and incomplete in documenting any of these various SNHL subtypes. The depth of investigation might have been dictated by the sophistication of the diagnostic tools available, as the first case of autosomal dominant SNHL was described almost a century ago.

Ormerod[5] in 1960 using histopathologic methods classified congenital dysplasias into four types: Michel, Mondini-Alexander, Bing-Siebenmann, and Scheibe. This classification has since been found to be deficient, as is evidenced by the newer classification schemes.[6,7] Despite this deficiency, it is interesting to note the adherence by clinicians to the use of eponyms and specifically that of Mondini. Macroscopic findings by Carlo Mondini[8] in 1791 have to be reconciled with findings of modern histologic and radiographic methods. Discrepancies in using restrictive traditional definitions will generate classification conflict as addressed by Valvassori et al.[9]

In this paper, we present a unique family in which three members were found to have various degrees of SNHL. Each involved subject underwent extensive laboratory evaluation to allow meaningful correlation of clinical findings. This family was found to have a type of autosomal dominant nonsyndromal SNHL that does not fit any of the previously described types. Furthermore, this report exemplifies the problems encountered in using traditional classification methods with particular reference to Mondini dysplasia.

FAMILY REPORT

The family being described has eight members, with the mother (patient 3), the youngest female sibling (patient 2), and the youngest male sibling (patient 1) involved with SNHL (Fig 1). The maternal side of the family is exclusively of Irish ancestry. Additional deceased maternal relatives in Ireland were reported to have hearing loss at a young age, but no additional clinical information is available. No characteristic or overt dysmorphic features were noted in the examination of the family members. Analysis by the medical geneticist at Children's Hospital of Pittsburgh indicated that the mode of transmission is autosomal dominant in nature. All unaffected family members underwent behavioral

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From the Department of Otolaryngology, University of Pittsburgh School of Medicine (Chan, Furman, Kamerer), and the Department of Radiology, St Clair Hospital (Eelkema), Pittsburgh, Pennsylvania.

REPRINTS — Kenny H. Chan, MD, Dept of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, One Children's Place, 3705 Fifth Ave at De-Soto St, Pittsburgh, PA 15213-3417.

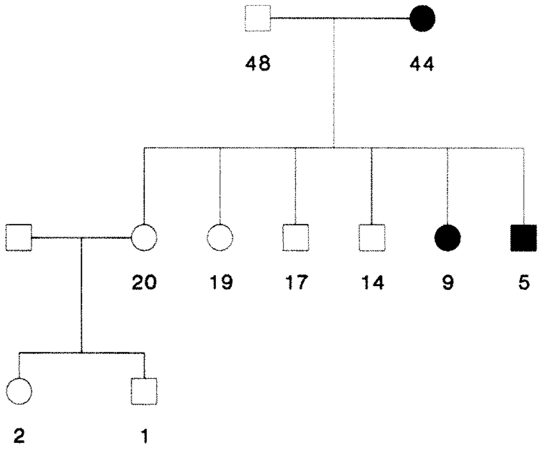


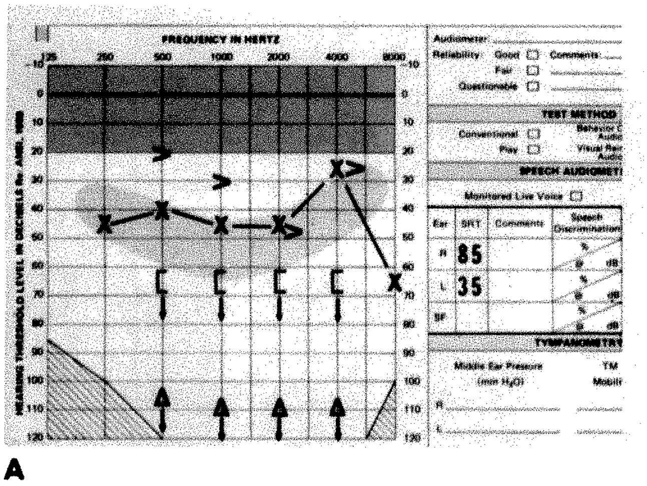
Fig 1. Family tree depicting unaffected members (open symbols) and members afflicted with hearing loss (filled symbols) with their respective ages.

audiometry and otoscopy and were found to have a normal hearing threshold and normal findings on otoscopic examination. The affected members will be discussed under the topics of clinical history, audiometry, radiography, and vestibular testing.

Clinical History. Patient 1 is a 5-year-old boy who presented at the age of 3½ with otitis media. His parents were concerned about speech delay and possible hearing loss. Otologic examination revealed lop ear, chronic effusion, and retraction pocket involving the left ear exclusively. He underwent tympanostomy tube placement for the latter two otologic findings. Because of persistent hearing loss on behavioral audiometry, an auditory brain stem response (ABR) was obtained and bilateral SNHL was confirmed. Computed tomography (CT) and vestibular testing were also performed.

Patient 2 is a 9-year-old girl who presented at the age of 8 with otitis media and right-sided hearing loss that had persisted for 1 year. She also underwent tympanostomy tube placement for persistent fluid. Subsequently, she completed CT and vestibular testing.

Patient 3 is a 44-year-old woman who has known about her own right-sided hearing loss since childhood. She was always under the impression that the hearing loss was the result of childhood mastoiditis for which she underwent a right mastoidectomy. Because of the diagnosis of SNHL in two of her children, she decided to investigate her hearing loss. She also underwent CT and vestibular testing. She is in relatively good health except for seborrheic dermatitis and hypoparathyroidism.



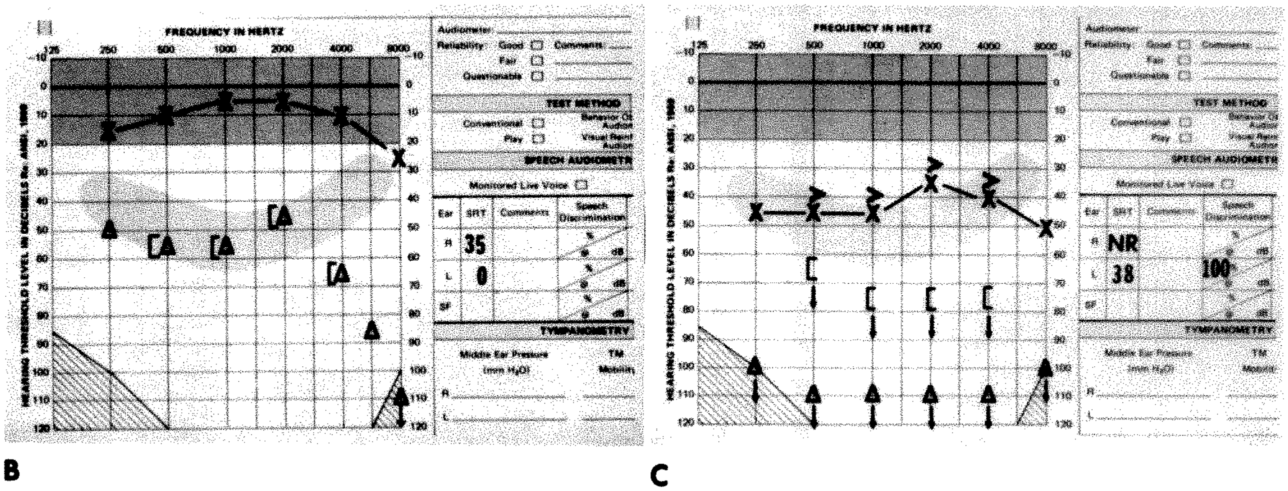


Fig 2. Audiograms of A) patient 1 (male sibling), B) patient 2 (female sibling), and C) patient 3 (mother).

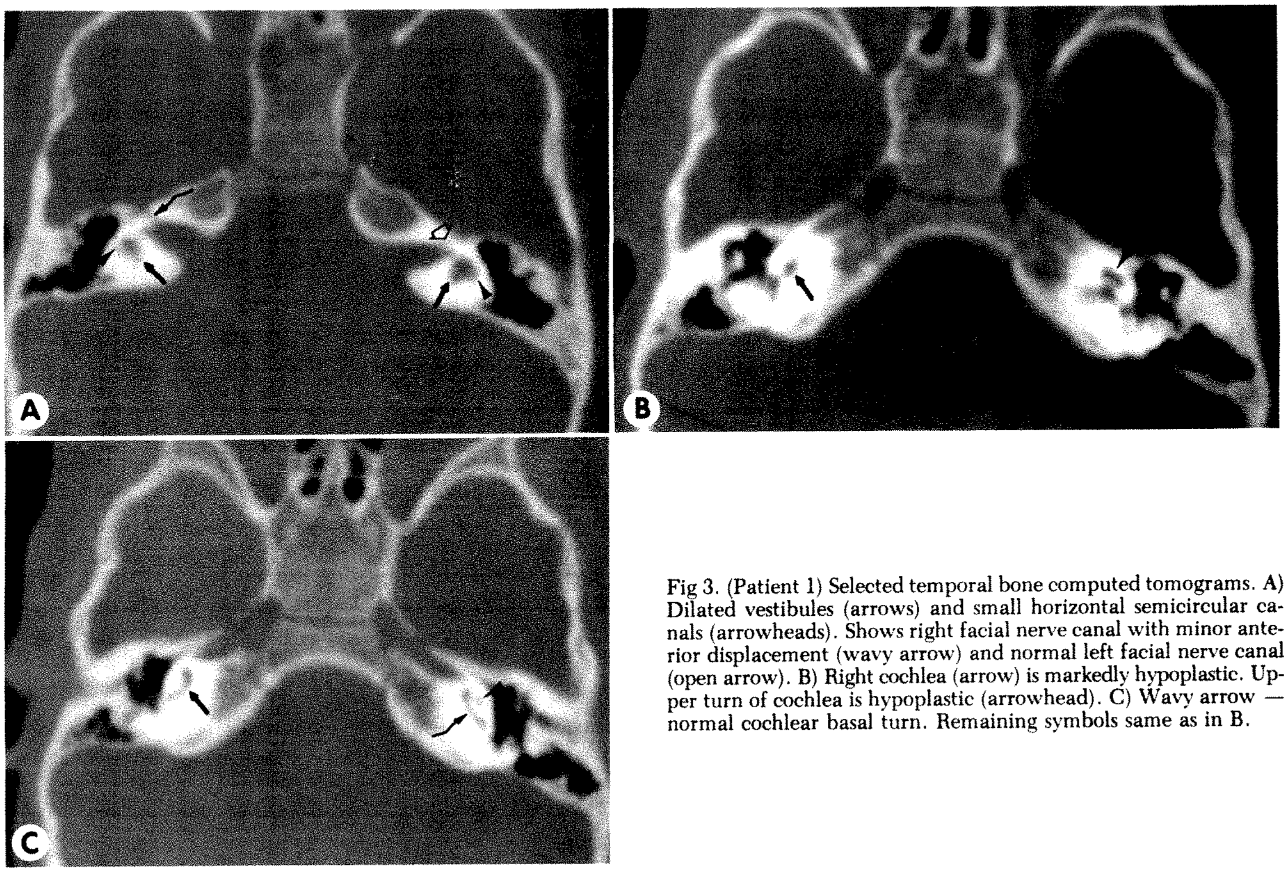


Fig 3. (Patient 1) Selected temporal bone computed tomograms. A) Dilated vestibules (arrows) and small horizontal semicircular canals (arrowheads). Shows right facial nerve canal with minor anterior displacement (wavy arrow) and normal left facial nerve canal (open arrow). B) Right cochlea (arrow) is markedly hypoplastic. Upper turn of cochlea is hypoplastic (arrowhead). C) Wavy arrow — normal cochlear basal turn. Remaining symbols same as in B.

Audiometry. Behavioral audiograms from the three subjects are shown in Fig 2. The results of the ABR indicated good correlation with the respective audiogram, and no evidence of retrocochlear involvement was noted. The male sibling, patient 1, was found to have profound SNHL in the right ear and moderate SNHL in the left ear (Fig 2A). This hearing loss was noted to have been stable for the past 3½ years. The female sibling, patient 2, has moderate SNHL in the lower frequencies and severe to profound SNHL in the higher frequencies in her right ear (Fig 2B). The hearing threshold in her left ear is normal. Her hearing loss has been stable for the past 2 years. The mother, patient 3, was shown to have profound SNHL in the right ear and mild to moderate SNHL in the left ear (Fig 2C). Although she complains of subjective fluctuation of her hearing in the left ear without associated vestibular symptoms, no clinical documentation has been established.

Radiography. On high-resolution CT (General

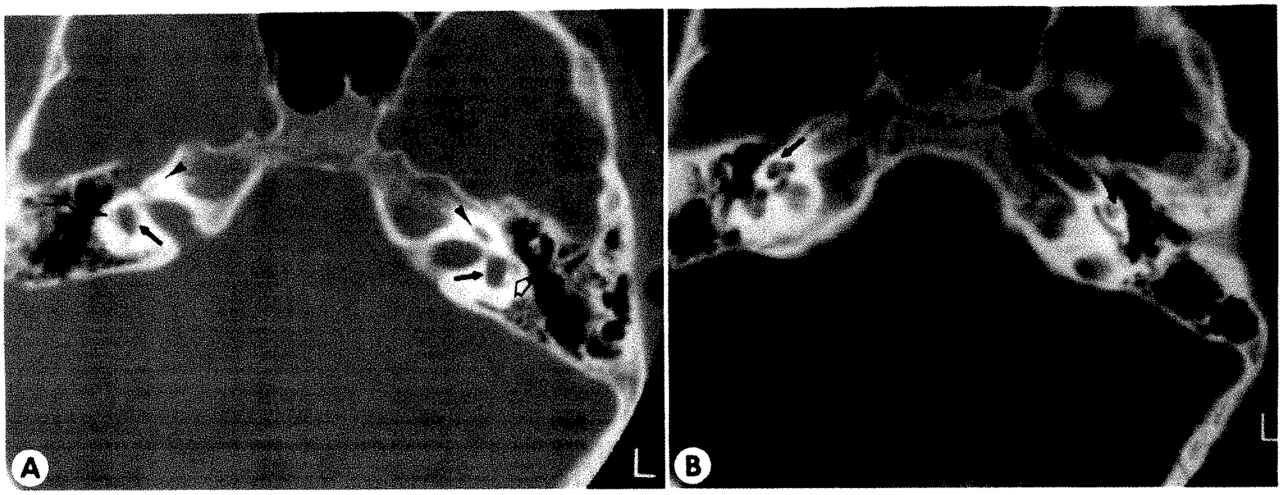


Fig 4. (Patient 2) Selected temporal bone computed tomograms. A) Dilated vestibules (arrows) and abnormal horizontal semicircular canals on left (open arrow) and right (wavy arrow). Arrowheads — normal cochleas. B) Slight bilateral flattering of apical turns of cochleas (arrows).

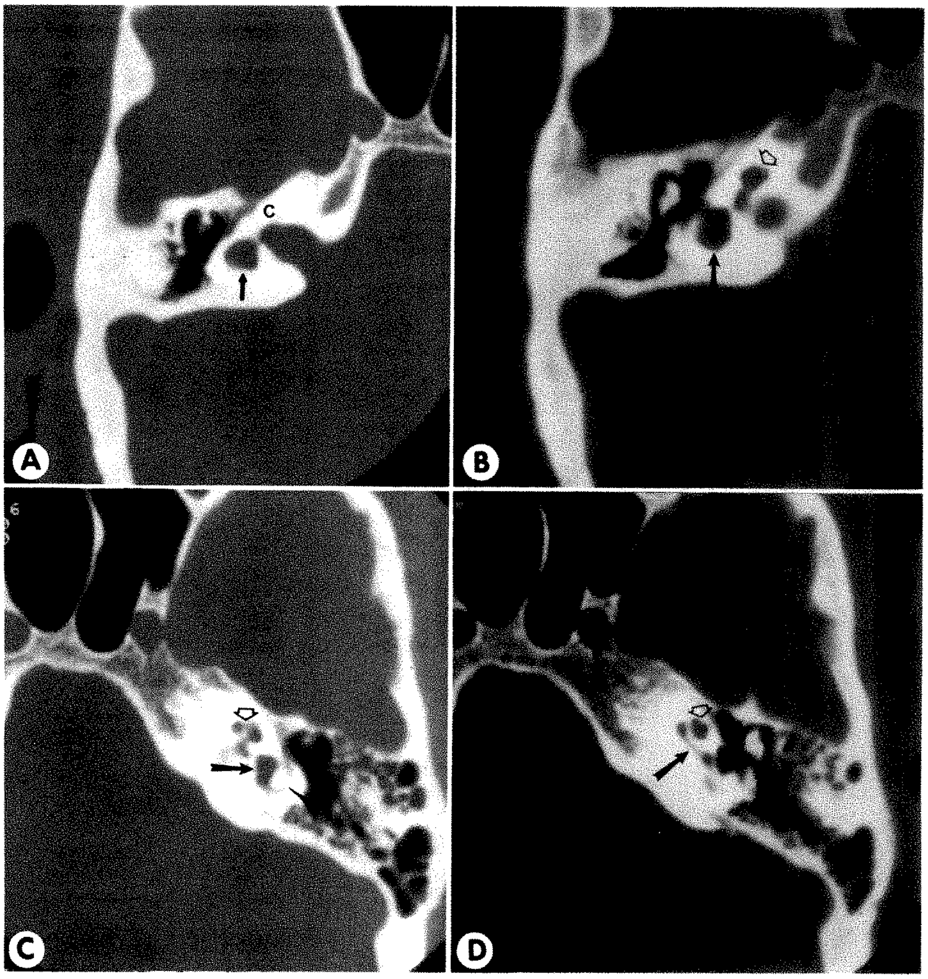


Fig 5. (Patient 3) Selected temporal bone computed tomograms. A) Vestibule and horizontal semicircular canals are merged into single cavity (arrow). C — usual location of normal cochlea. B) Merged vestibule (arrow). Open arrow — cochlea. C) Left vestibule (arrow) is slightly dilated. Arrowhead — horizontal semicircular canal, open arrow — cochlea. D) Normal basal turn of left cochlea (arrow) is partially imaged. Upper turns (open arrow) lack segmentation.

Electric 9800), 1.5-mm-thick axial sections were obtained through both temporal bones in all subjects. Selected images of patient 1 are shown in Fig 3. In Fig 3A both vestibules (arrows) are dilated, and each shares a common cavity with the abnormally small horizontal semicircular canal (HSCC). The labyrinthine portion of the right facial nerve canal shows minor anteromedial displacement as compared to the normal left canal. This type of anomalous facial nerve canal configuration has been described as associated with cochlear hypoplasia.[10] In Fig 3B,C (3.0 mm and 4.5 mm inferior to Fig 3A), the right cochlea is markedly hypoplastic, consisting of a basal turn that ends in a small rudimentary sac. On the left, the cochlear basal turn is normal, but the upper turns are hypoplastic.

Representative images from patient 2 are shown in Fig 4, which shows bilateral inner ear anomalies. In Fig 4A the vestibule is dilated bilaterally. The left HSCC is a complete ring but is abnormally small. The small right HSCC is merged with the vestibule. The demonstrated portion of each cochlea is normal. The right ear is imaged at a slightly higher level than the left in Fig 4B (3.0 mm inferior to Fig 4A). Except for the flattening of the apical turn bilaterally, which may be projectional, the cochleas (arrows) are normal.

The bilateral congenital malformations in the temporal bones of patient 3 are illustrated in Fig 5. In Fig 5A, the vestibule and HSCC in the right ear are merged into a single cavity. The hypoplastic cochlea does not extend into this level, and the normal location is indicated. In Fig 5B (1.5 mm inferior to Fig 5A) the merged vestibule is again seen. The cochlea is dilated and lacks normal segmentation. Figure 5C shows the left vestibule to be slightly dilated. The HSCC is well formed. The cochlea is normal at this level. The normal basal turn of the left cochlea is partially imaged in Fig 5D. The upper turns lack segmentation.

Vestibular Testing. Patient 1 had rotational testing results consistent with reduced vestibular function bilaterally. There was no other vestibular laboratory testing available. Patient 2 had a left directional preponderance and a reduced left vestibular response on caloric testing. Total response magnitude was low. Her results on rotational testing were within normal limits although they showed borderline low-amplitude responses. Positional testing and ocular motor testing, however, revealed a left-beating spontaneous vestibular nystagmus. Results on dynamic posturography (Equitest) testing were also consistent with a vestibular system abnormality. Patient 3 had normal ocular motor function and normal static positional testing results. Caloric testing indicated absent responses bilaterally. Rotational testing revealed that responses could be elicited; however, they were of reduced magnitude and showed a left directional preponderance. Dynamic posturography results were abnormal, consistent with a vestibular system abnormality.

DISCUSSION

In this report, three members of a family with autosomal dominant SNHL without associated abnormalities are described. Because of the degree of involvement in terms of severity and laterality of the three members, this family does not fit into any of the established types of hereditary hearing loss with no associated abnormalities summarized by Konigsmark and Gorlin.[2] Early-onset dominantly transmitted SNHL, which most closely resembles the disorder of the family described herein, generally presents in the first or second decade of life and is associated with progressive symmetric SNHL with preservation of frequencies below 2,000 Hz. Contrary to the symmetric pattern, the two siblings have asymmetric SNHL. Contrary to the progressive pattern, the mother still has serviceable hearing in the left ear.

In reference to the term "Mondini dysplasia" this family report is unique. Inasmuch as the authors recognize the shortcomings of using eponyms, they herein accept the notion that Mondini dysplasia represents a spectrum of osseous and membranous dysplastic changes within the temporal bone that can be evaluated by either histopathologic or radiographic methods. Since this clinical term is so ingrained in the otologic literature, to conform to this definition and the usage of this term is necessary for the purpose of discussion. Mondini[8] described the first case of combined bony and membranous dysplasia of the inner ear in an 8-year-old boy born deaf. The most striking abnormality in this child was a shortened 1½ turns of the cochlea, and the minor anomalies included a dilated vestibular aqueduct and an enlarged vestibule. The inner ear malformations of the subjects in our report all share various degrees of cochlear arrest bilaterally. In addition, the more distinctive radiographic findings of the merged HSCC and the enlarged vestibule are demonstrated in all three subjects. All of these changes are compatible with the traditional as well as the broader definition of Mondini dysplasia. From a historical point of view, the other types of dominant SNHL described by Konigsmark and Gorlin might have shared some of these radiographic changes had advanced imaging techniques been available.

In his treatise on Mondini malformation, Schuknecht[11] methodically characterized this entity as part of a syndrome or as an isolated occurrence. Clearly, the inner ear malformations observed in this family fall under the isolated occurrence classification. There is a plethora of reports in the world literature on the various clinical aspects of Mondini dysplasia associated with syndromes such as Klippel-Feil[12] and Pendred's.[13] No meaningful reports regarding familial Mondini dysplasia occurring in isolation were found through our literature search. In his survey of the literature, Illum[14] noted two Danish reports published in the late 1880s that noted that two of five children with Mondini dysplasia were siblings. Since these two reports contained no useful clinical information, whether Mondini dysplasia occurred as a syndrome or in isolation in these two children will never be known. In the authors' view, the present report represents the first in-depth clinical study of a family with nonsyndromal Mondini malformation.

From a radiographic standpoint, a spectrum of inner ear pathologic changes was noted for each patient. In all temporal bones, both the cochlear and the vestibular systems were involved to some degree. No associated vestibular, cochlear aqueductal, or internal auditory canal anomalies were noted. There was excellent correlation between the degree of cochlear derangement and the severity of hearing loss with the exception of the right ear of patient 2, which showed only flattening of the apical turn on CT but moderate SNHL in the middle frequencies and severe loss in the high frequencies. Each of the patients had abnormal vestibular function indicating reduced vestibular sensitivity bilaterally; this finding correlates well with the bilateral vestibular structural abnormalities in each patient. Of particular note is that patient 2 had a left reduced vestibular response on caloric testing in association with a small left HSCC seen on CT.

In general, there was good correlation between hearing sensitivity and vestibular sensitivity in that each patient had both hearing loss and reduced vestibular function. Patient 3 had both absent caloric responses and bilateral hearing loss. One discrepancy noted between audiometric and vestibular testing was that for patient 2 hearing was normal on the left. This disparity between vestibular and audiometric testing is consistent with the discrepancy between the structural abnormalities of this patient's vestibular and auditory apparatuses.

This report describes a multidisciplinary clinical approach to the study of congenital and genetic deafness. Histopathology remains the gold standard for definitive postmortem examination of the temporal bone and especially the membranous portion. Current premortem technology allows an accurate study only of the osseous portion of the otic capsule. A large-scale correlative study using a similar strategy may yield valuable information to further the understanding of and the management of congenital and genetic hearing loss.

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Ann Otol Rhinol Laryngol 100:1991

TETANIC RESPONSE OF THE CRICOTHYROID MUSCLE

FARIBORZ ALIPOUR-HAGHIGHI, PHD
ADRIENNE L. PERLMAN, PHD INGO R. TITZE, PHD
IOWA CITY, IOWA

Tetanic response of canine cricothyroid muscle tissue was investigated through a series of experiments conducted in vitro. Two separate portions of the cricothyroid muscle, namely the pars recta and pars oblique, were studied. Samples of the muscle were dissected from dog larynges excised a few minutes before death and kept in Krebs-Ringer solution at a temperature of 37° ± 1°C and a pH of 7.4 ± 0.05. Tetanic contraction of the muscle samples was obtained by field stimulation to the muscle through a pair of parallel-plate platinum electrodes and with a train of square pulses of 0.1-millisecond duration and 85-V amplitude. Isometric force responses of the pars recta and pars oblique muscles were obtained electronically with a dual servo system (ergometer). The effect of tissue elongation on the active and passive responses was quantified by stimulation of the sample during cyclic elongation. Both active and passive responses as a function of elongation were obtained on the same sample.

KEY WORDS — canine larynx, cricothyroid muscle, isometric force response, tetanic contraction.

INTRODUCTION

Quantitative data on the physiologic properties of laryngeal muscles are important to both clinicians and researchers. To the clinician who is engaged in surgical treatment of laryngeal disease, the data are important because techniques for muscle reinnervation[1,2] may include attempts to reproduce, as closely as possible, such physiologic characteristics as muscle contraction time, muscle relaxation time, and nerve conduction velocity. Knowledge of such physiologic properties in nondiseased laryngeal muscles is important when applying the techniques of electrical stimulation and electromyography to the diagnosis of laryngeal disease.[3] Researchers studying the effects of transcutaneous stimulation of the larynx have been aware of this and have found muscle response characteristics that are compatible with data previously obtained on contraction times of certain laryngeal abductor and adductor muscles.[4] A better knowledge of active and passive properties of the different portions of the cricothyroid muscle would not only enhance our understanding of the normal function of this muscle and dynamics of the larynx, but may also be useful in the analysis of neurologic jitter in phonation[5] and in preliminary research on laryngeal pacing.

Additionally, the contractile properties of laryngeal muscles have been shown to be important in the development of physiologically based models of phonation[6,7] and the formulation of the body-cover theory of phonation.[8,9] An awareness of the need for research to quantify the physiologic and biomechanical properties of the laryngeal muscles has become increasingly evident. Of particular interest are the properties of thyroarytenoid and cricothyroid muscles, the muscles principally responsible for the control of the fundamental frequency of phonation.

The cricothyroid muscle elevates the cricoid ring with its more vertical portion (pars recta), and causes a retraction of the cricoid cartilage with respect to the thyroid cartilage with its more horizontal portion (pars oblique).[10] The primary function of the cricothyroid muscle, which is control of the length and tension of the vocal fold, is achieved by tetanic contraction of the pars recta (causing unilateral elevation of the cricoid ring or rotational movement) and pars oblique (causing a ventrodorsal gliding). According to Vilkman,[11] 30% to 40% of the elongation in vocal folds is due to the gliding of the cricoid cartilage. Furthermore, this rotation and gliding of the cricoid play an important role in adduction and abduction of the vocal folds.[10,11]

The magnitude of passive and active contractile muscle forces and the time-related characteristics such as speed of contraction and contraction period are needed in the development of theoretic models that describe dynamic behavior in the regulation of pitch and register. To that end, a series of in vitro experiments were conducted in our laboratory to study the active and passive properties of the vocalis muscle and cricothyroid muscles. A canine model was used throughout these experiments.

Active properties of the vocalis muscle have been reported on twitch and tetanic contraction.[12,13] Twitch characteristics of the cricothyroid muscle were studied by Perlman and Alipour-Haghighi.[14] They reported on the contraction and half-relaxa-

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From the Voice Acoustics and Biomechanics Laboratory, Department of Speech Pathology and Audiology, Wendell Johnson Speech and Hearing Center, The University of Iowa (Alipour-Haghighi, Titze), and the Audiology and Speech Pathology Service, Veterans Administration Medical Center (Perlman), Iowa City, Iowa. This study was supported by National Institutes of Health/National Institute of Neurological and Communicative Disorders and Stroke grant NS 16320-08. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of The University of Iowa.

REPRINTS — Fariborz Alipour-Haghighi, PhD, Voice Acoustics and Biomechanics Laboratory, Dept of Speech Pathology and Audiology, Wendell Johnson Speech and Hearing Center, The University of Iowa, Iowa City, IA 52242.

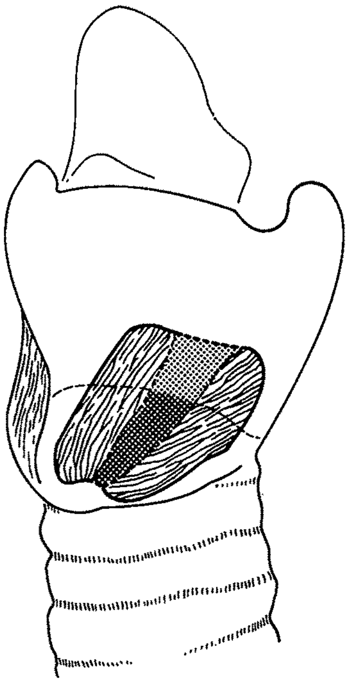


Fig 1. Schematic of canine larynx and its cricothyroid muscles.

tion time of the pars recta portion of this muscle as a function of elongation. Although twitch response data provide information on the speed of contraction of this muscle, study of the cricothyroid muscle during sustained phonation requires knowledge of its characteristics during tetanic contraction. The purpose of the present study was to quantify the active tetanic and passive force of the different portions of the cricothyroid muscles in the isometric state. The questions that are posed in this study are as follows.

1. What is the maximum active-to-passive ratio generated in the pars recta and pars oblique portions of the cricothyroid muscle and how does it vary at different levels of elongation?
2. What is the time course of tetanic contraction in the cricothyroid muscle with respect to onset and offset of stimulation?

METHOD

Samples of cricothyroid muscle tissue were dissected and prepared from viable excised larynges of 18 large dogs weighing 20 to 25 kg. One or two samples of the pars recta portion from one side and one or two samples of the pars oblique portion from the contralateral side of the larynx were prepared. These two portions are not easily isolated; to some degree they seem like one muscle with an exterior length of 17 to 20 mm and a width of 20 mm, with fibers that run with an angle of about 60° with respect to the midsagittal plane (Fig 1). To assure distinction between the samples, the most medial bundles were used for the pars recta samples and the most lateral portion was used for the pars oblique samples. As shown in Fig 1, these muscle bundles run between exterior surfaces of the thyroid (light dotted area) and cricoid (dark dotted area). Since these two surfaces form a large angle, the cricothyroid muscle has longer fibers on the exterior portion and much shorter fibers adjacent to the cricothyroid ligament. Thus, preparations were made only from a 2- to 3-mm depth (from the exterior surface toward the cartilages) and a 3- to 4-mm width (lateral dimension). Small pieces of thyroid and cricoid cartilage were retained at the ends of each sample for natural boundary attachments. Tevdek (2-0) polyester suture was threaded through these cartilages. The samples were maintained in Krebs-Ringer solution and aerated with 95% oxygen and 5% carbon dioxide. The samples were mounted in a water-jacketed organ bath chamber containing the electrolyte solution and were maintained at a temperature of 37° ± 1°C and a pH of 7.4 ± 0.05 during the experiment. Force and elongation of the samples were controlled and measured with a dual servo system (Cambridge Technology, model 305 ergometer). Before dissection, the longest and the shortest fibers of the sample were identified and measured to obtain an approximate average length of each sample in situ. Samples were mounted vertically in the chamber, with the approximate average length set as close to the previously measured in situ length as it could be without any slack in the suture. This generally required an initial force of 1 to 3 g on the pars recta sample and 2 to 5 g on the pars oblique samples.

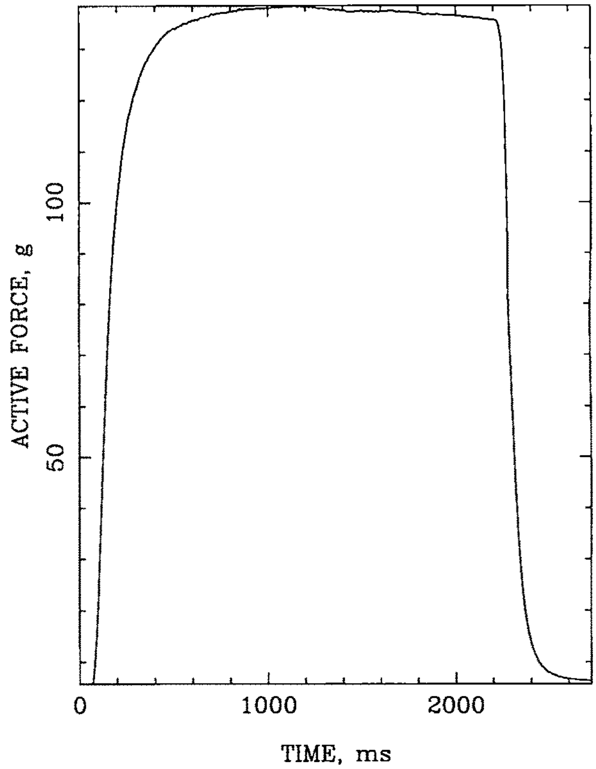


Fig 2. Typical tetanic response of cricothyroid muscle. Stimulation was applied for about 2 seconds at 65 Hz.

Data for the active properties were obtained by

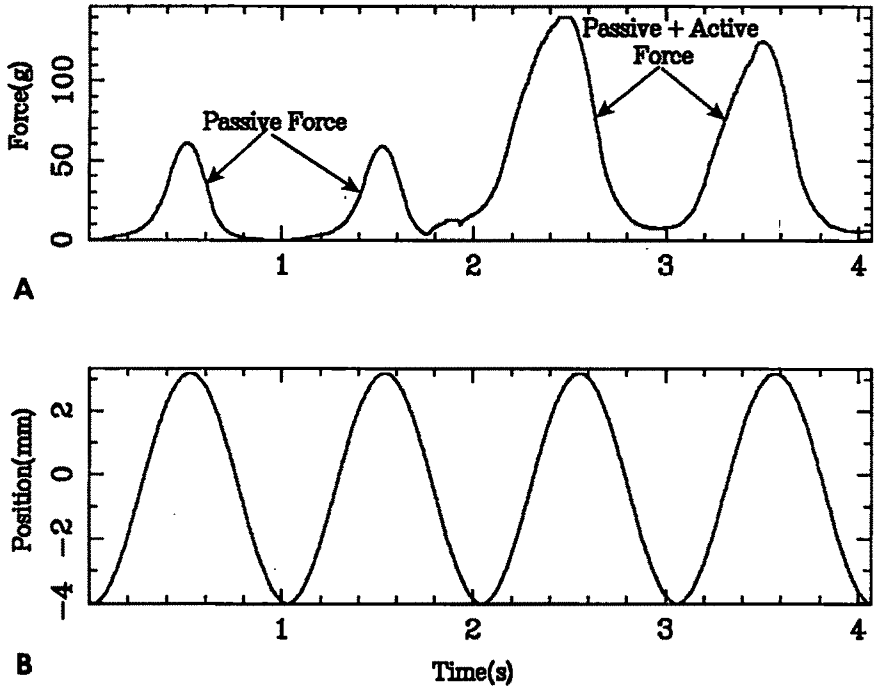


Fig 3. A) Force response of muscle due to B) sinusoidal elongation. Stimulation was turned on after three cycles of passive stretch and release.

application of electrical field stimulation to the muscle through a pair of parallel-plate electrodes with a platinum surface positioned around the muscle. Tetanic contraction of the muscle was initiated by application of a train of square pulses of 0.1-millisecond duration and 85-V amplitude at a frequency of 65 Hz transverse to the muscle fibers. The fusion frequency reported by Sato and Hisa[15] and Hast[16] was 40 Hz for the cricothyroid; however, we found a variability in the fusion frequency that ranged between 45 and 65 Hz for the pars recta and pars oblique portions. Thus, in order to ensure fusion in both samples, a stimulation rate of 65 Hz was used.

RESULTS

Figure 2 shows a typical tetanic response of the cricothyroid pars recta muscle portion as a function of time. For the type of artificial stimulation applied, the response has a rising leg that takes up to 500 milliseconds to reach the maximum active force, a slowly decreasing tetanic force that is dependent upon the strength of electrical stimulation, and a falling leg that occurs when stimulation is stopped and the muscle relaxes to its passive force. This relaxation might take up to 300 milliseconds. The maximum tetanic force depends on the size of the muscle sample and its elongation. In order to quantify the maximum tetanic force at various elongations and eliminate the effects of sample size, one can normalize this active force with respect to its passive force and obtain a maximum active-to-passive ratio. One method of obtaining the maximum active-to-passive ratio of the muscle is to elongate each sample in a stepwise fashion and then stimulate after each elongation. This results in a force after passive elongation summed to the tetanic force (Fig 2). Alipour-Haghighi et al[13] reported data on the thyroarytenoid muscle with that measurement protocol.

We used a somewhat different technique to generate force-elongation curves in this study. Instead of stepwise elongation, each sample was subjected to a slow stretch and release. To generate a slow

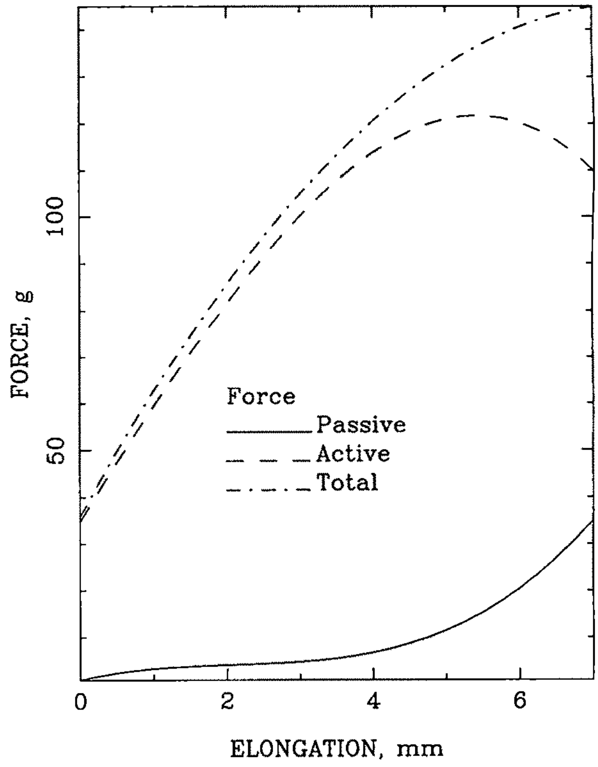


Fig 4. Passive, active, and total force response of muscle sample extracted from typical data represented by Fig 3 as function of elongation.

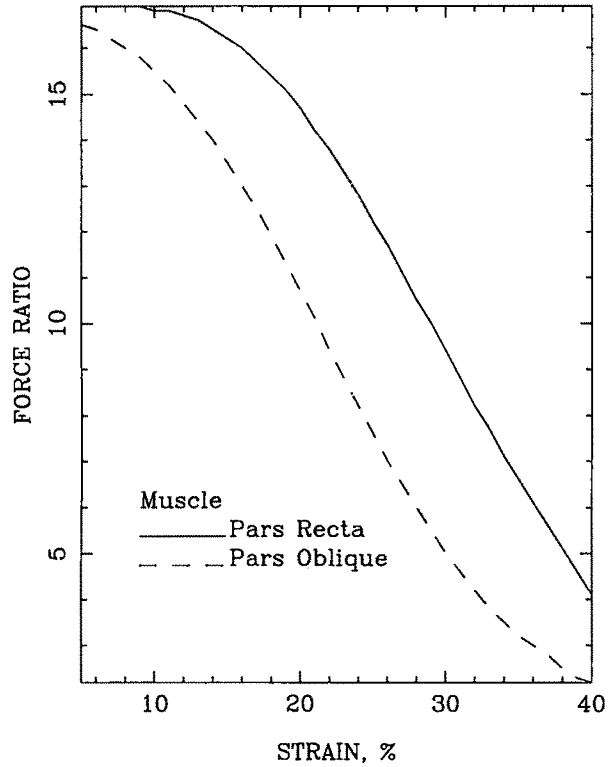


Fig 5. Averaged maximum active-to-passive ratio of cricothyroid muscles.

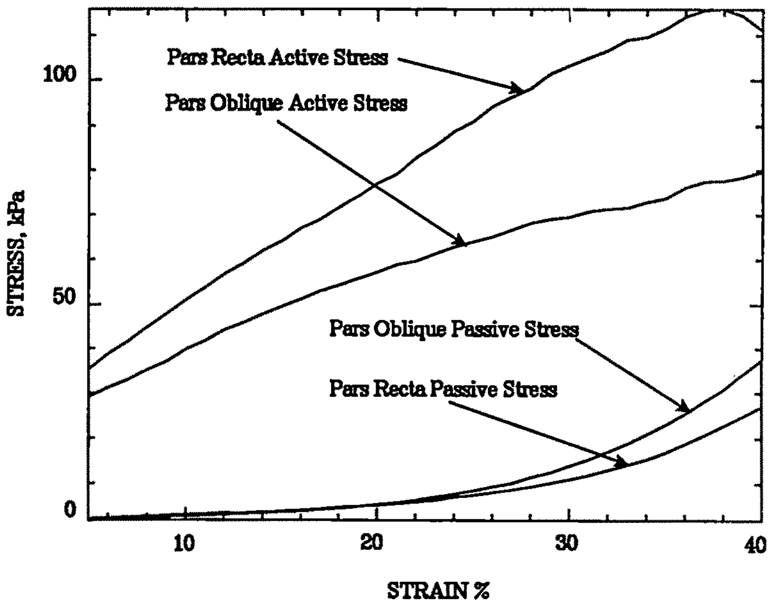
stretch and release, a sinusoidal voltage was applied to the ergometer at a frequency of 1 Hz. This passive force response of the muscle was observed to vary at the same frequency (Fig 3A) as the elongation (Fig 3B). After a few cycles for preconditioning (to allow for passive relaxation), a field stimulation was applied for 3 to 4 seconds; the generated active force was superimposed on the passive force of the muscle. By subtracting the passive response from total response, the maximum active force together with the sample elongation was obtained. Advantages of this technique are that the maximum active-to-passive ratio is independent of the sample's cross-sectional area and its irregular shape, and that by decreasing the length of the experiment, the opportunity for decomposition of the muscle is decreased. In Fig 3A, the passive cycle is identified on the left and the passive plus maximum active cycle on the right; both were obtained from the same sample.

Figure 4 shows typical active and passive force responses for the pars recta sample obtained with the method we have described. Initially, the passive force did not increase very much; but after a 15% elongation (about 3 mm), it increased more rapidly. This could be due to the existence of collagen fibers that straighten first and orient in the direction of elongation. Unlike the passive force, the active force increased rapidly with elongation. The typical rate of change of active force was about 20 g/mm. Once elongation reached a maximum at about 5 to 6 mm (25% to 35% strain), the active force began to decrease.

The maximum active-to-passive ratio was obtained by dividing the active force and passive force in Fig 4. To average the maximum active-to-passive ratio across the samples, the elongation was normalized to the average length of the sample; this provided a measure of strain. Figure 5 shows maximum active-to-passive ratios of pars recta and pars oblique muscles averaged over six samples for each portion.

Figure 6 shows the passive and maximum active stress (force per unit area) of the pars recta and pars oblique muscles. The active and passive stresses are obtained by normalizing the passive and active forces to the cross-sectional area. Results were averaged over nine samples of pars recta and eight sam-

Fig 6. Averaged passive and maximum active stress-strain curves of cricothyroid muscles.



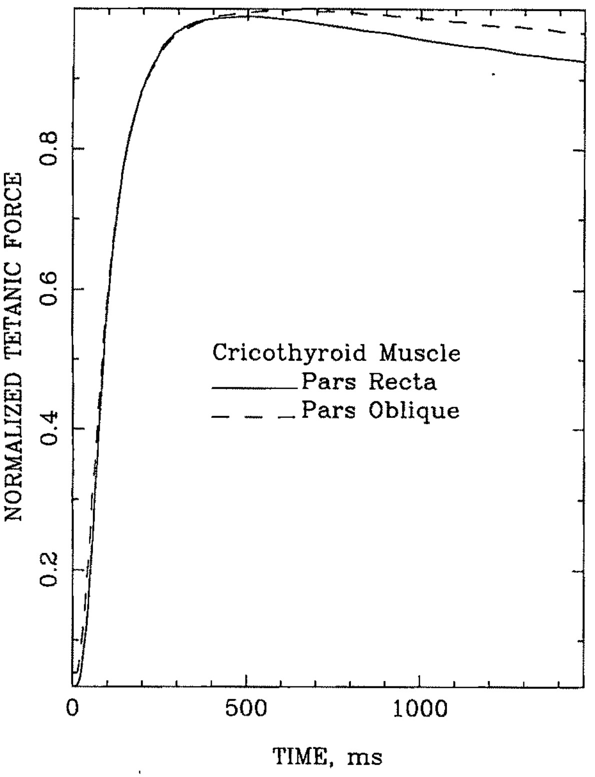


Fig 7. Averaged tetanic contraction time of cricothyroid muscles.

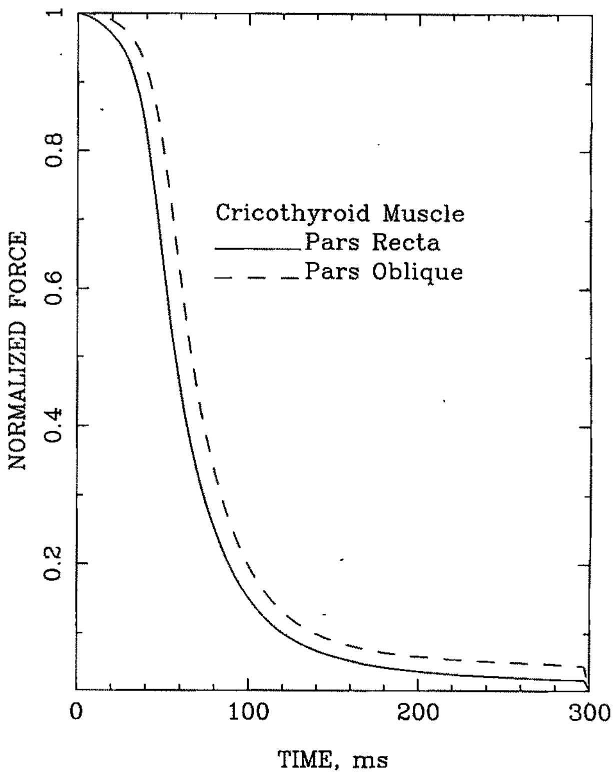


Fig 8. Averaged tetanic relaxation time of cricothyroid muscles.

ples of pars oblique. The passive responses of the two muscle portions are very similar, especially at low strain values. However, with active stress responses, the pars recta portion produced more active force per unit area.

The time course of tetanic contraction was studied through the averaging of the tetanic contraction data, similar to the data in Fig 2. However, to have a meaningful average, the rising legs of the different samples were normalized to the maximum tetanic force. Figure 7 shows averaged tetanic contraction curves for the pars recta and pars oblique portions (six samples each). Below a 97% force level, both muscles show the same contraction time course. The time required to reach a maximum tetanic force may be about 500 milliseconds. However, in prephonatory conditions cricothyroid muscles may not generate a maximum isometric response. Rather, they act in an isotonic state and with a tetanic force of much less than the maximum value. For example, in order to generate 90% of maximum tetanic force it takes about 200 milliseconds; but to generate 50% of the maximum force, the contraction takes only about 100 milliseconds.

The falling leg of tetanic contraction data was normalized in a fashion similar to that of its rising leg and was averaged over six samples of each muscle (Fig 8). There is a little difference between the relaxation curves of the two portions of cricothyroid muscle. While a complete relaxation might take over 200 milliseconds, a 50% relaxation might take only less than 60 milliseconds.

DISCUSSION

This study reported active and passive force-elongation data on the two separate portions of the cricothyroid muscle. The biomechanics of cricothyroid articulation is a key mechanism in control of pitch and amplitude of vocal fold vibration. These data are expected to be very useful in quantitative modeling of pitch control, in which rotational and gliding dynamics of the thyroid and cricoid cartilages around the cricothyroid joint is a key problem that needs to be solved. Data on maximum active force produced by intrinsic laryngeal muscles will define the available torques and gliding force for relative movement between the cartilages, which in time will determine changes in vocal fold length.[9] The results on response time will help determine the speed with which pitch and register changes can be executed in phonation.

The reported data for maximum tetanic contraction, when all the fibers produce their isometric active force, could be considered as the limiting parameter. The cricothyroid muscle usually acts in an isotonic mode and decreases its length during contraction. This decrease of length could reach up to 50% at high pitches.[10] Furthermore, in the singer's chest voice, the activity of the cricothyroid muscle is proportional to the fundamental frequency and only in falsetto register could reach its maximum.[10,17]

The time course of tetanic contraction reported here indicated that these muscles may take about 200 milliseconds to reach 90% of maximum tetanic contraction. Their contraction time for 50% of that maximum force is about 100 milliseconds. This range of contraction is close to what is reported by Faaborg-Andersen[18] on the time interval between the onset of the change of an action potential pattern and the onset of a tone recorded by a microphone in the cricothyroid muscle during phonation. The active relaxation data may be related to the pitch-lowering period during singing.

The cricothyroid muscle is a robust muscle, capable of producing strong active and passive forces with elongation. A maximum active force (fused tetanus) in the pars recta may reach up to 1,000 times the weight of the sample at 40% to 50% elongations. Similarly, the active force for the pars oblique may reach up to 700 times its weight at comparable elongations.

Results of this study also suggest that force in this muscle is highly sensitive to a change in length. This sensitivity is useful, particularly when the cricothyroid muscle is used to control tension and to assist in control of glottal geometry and adduction in the vocal folds.

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ORAL OFLOXACIN THERAPY FOR INVASIVE EXTERNAL OTITIS

DANIEL ZIKK, MD
YORAM RAPOPORT, MD
ITAMAR SHALIT, MD
CHAIM REDIANU, MD
MORDECHAI Z. HIMMELFARB, MD
TEL AVIV, ISRAEL

The clinical efficacy and safety of orally administered ofloxacin (400 mg twice daily) were evaluated in 24 adult patients (17 men and 7 women; mean age, 65.8 years) with pseudomonal invasive external otitis (IEO). The patients were divided into two groups: group A, (n = 9) suffering from a mild form of IEO, and group B (n = 15), suffering from a more severe form of the disease. Diabetes mellitus was the main underlying disease in these patients. *Pseudomonas aeruginosa* was the only pathogen in 18 infected ears and part of the polymicrobial flora in an additional 6. Cure was observed in 83.3% of the patients. Two of the cured patients required more than one course of ofloxacin treatment. Development of *P aeruginosa* resistant to ofloxacin (n = 3) and severe allergic reaction (n = 1) required the discontinuation of ofloxacin therapy. Other side effects such as nausea, arthralgia, and vaginal itching were minimal. Oral administration of ofloxacin seems to be an effective, convenient, relatively safe, and economical therapy of IEO caused by the susceptible organism.

KEY WORDS — fluoroquinolones, malignant external otitis, ofloxacin.

INTRODUCTION

Invasive external otitis (IEO) is an aggressive form of external otitis usually occurring in elderly diabetic patients. The disease begins as an innocuous infection of the squamous epithelium of the external ear canal. It may progress to the underlying soft tissue, cartilage, blood vessels, or bone, leading eventually to cellulitis, chondritis, or osteomyelitis of the temporal bone. Uncontrolled disease may lead to osteomyelitis of the base of the skull, multiple cranial nerve palsies, meningitis, and death.[1,2]

Pseudomonas aeruginosa is uniformly the primary causative pathogen in IEO. Although the precise pathogenesis of IEO is not fully understood, the invasive course of the disease has been attributed to the combination of several factors. These include host factors such as poor local tissue perfusion and defective immunity of elderly patients with longstanding diabetes. In addition, *P aeruginosa* may activate several cytotoxic extracellular substances that have the power to cause severe tissue damage to the host.[3]

The current recommended treatment for IEO consists of the combination of systemically administered aminoglycosides and a β-lactam agent and of local surgical debridement. This combined therapy should be administered for at least 4 to 6 weeks.[4,5] Such a therapy in elderly diabetic patients involves the risks of prolonged hospitalization, prolonged use of intravenous catheters, and the side effects of the antibiotics. The aminoglycosides may affect renal and inner ear function, while the broad-spectrum penicillins may cause hypersensitivity reactions, bleeding, and sodium overload.[6,7]

Ofloxacin is a new fluorinated 4-quinolone derivative with a broad antimicrobial spectrum of activity. The agent is bactericidal, since it inhibits the activity of DNA-gyrase, which is an essential bacterial enzyme in DNA replication. Fluoroquinolones such as ofloxacin and ciprofloxacin are the first oral antimicrobial agents with significant activity against *P aeruginosa*. Their spectrum of activity includes most of the pathogenic gram-negative organisms and, to a lesser degree, important gram-positive pathogens such as staphylococci and streptococci.[8,9] The fluoroquinolone antibiotics may be useful agents for the treatment of IEO, since they have excellent activity against gram-negative bacilli, demonstrate favorable pharmacokinetic properties after oral administration, and are effective in the treatment of bone and soft tissue infections.[10-12]

This study was designed to evaluate both the efficiency and the safety of orally administered ofloxacin in the treatment of IEO.

PATIENTS AND METHODS

The study was conducted as a prospective, open-label, noncomparative study.

Enrollment Criteria. Patients were eligible to participate in the study if they fulfilled the following inclusion criteria.

1. Adults, 18 years of age or older, of either sex, suffering from external otitis unresponsive to topical antibiotic treatment for at least 10 days.
2. Presence of granulation tissue located at the posterior-inferior canal wall or at the junction of the osseous-cartilaginous external ear canal.

From the Department of Otorhinolaryngology (Zikk, Rapoport, Redianu, Himmelfarb) and the Infectious Diseases Unit (Shalit), Tel Aviv Sourasky Medical Center, Ichilov Hospital, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

REPRINTS — Daniel Zikk, MD, Dept of Otorhinolaryngology, Tel Aviv Sourasky Medical Center, Ichilov Hospital, 6 Weizman St, Tel Aviv 64239, Israel.

3. Isolation of *P aeruginosa* (as a single isolate or in combination with other pathogens) in cultures obtained from affected ear canal.
4. Erythrocyte sedimentation rate (ESR) of ≥40 mm/h upon enrollment.

Exclusion Criteria.

1. Female patients in whom the possibility of pregnancy could not be excluded with certainty or who were nursing.
2. Patients with a known hypersensitivity to nalidixic acid or newer quinolones.
3. Patients with severe renal impairment (serum creatinine level greater than 3.0 mg/dL).
4. Patients with either central nervous system diseases or psychiatric disease.

Severity of Infection. Enrolled patients were divided into two groups according to the severity and extent of the infection. Group A included patients who met all the enrollment criteria but had no clinical signs or radioisotopic (Tc 99) scan findings of temporal bone involvement. These patients were considered as having a mild form of IEO. Group B included patients with IEO and clinical and/or isotopic scan evidence of temporal bone involvement, ie, marked tracer accumulation in the temporal bone ipsilateral to the affected ear. These patients were considered as having a severe form of IEO.

Dosage, Administration, and Drug Compliance. Ofloxacin is registered and approved for clinical use in Israel. Ofloxacin was given orally at a dose of 400 mg twice daily at an approximately 12-hour interval (total daily dose of 800 mg). The drug was taken 2 hours before or 2 hours after a meal. Group A patients were hospitalized for 10 to 30 days (average, 19 days) and group B for 21 to 69 days (average, 32 days). Thereafter, the patients were treated at the outpatient clinic. During hospitalization, ofloxacin was administered by the staff nurses. Outpatient drug compliance was monitored by tablet counts at weekly office visits, by telephone interview, or by the outpatient home care service.

Adjunctive Therapy. The therapeutic adjuncts used routinely in the otorhinolaryngology department for patients with IEO were permitted in the enrolled patients. These included application of topical gentamicin sulfate or tobramycin sulfate drops (3 mg/mL) as well as surgical debridement of granulation tissue and sequestra.

Clinical and Laboratory Tests Upon Enrollment. Prior to ofloxacin administration each patient provided a detailed medical history and underwent a complete physical and otolaryngologic examination. Otoscopy was carried out with a surgical otomicroscope. Specimens for bacterial and fungal cultures were obtained from purulent ear drainage prior to enrollment. Each patient underwent the following laboratory tests on enrollment: complete blood count, ESR (Westergen), blood glucose and electrolytes, renal and liver function, prothrombin time, and urinalysis. Standard radiographs of the temporal bones and bone scanning with Tc 99 were obtained in all patients during the first few days of treatment. Computed tomography of the skull and temporal bone was performed when clinically indicated. Tuning fork and pure tone audiometry tests (bone conduction only, to avoid contamination of the equipment) were performed in all patients upon enrollment.

Pus, exudate, and samples of granulation tissue for culture were taken through a sterile ear speculum that was inserted into the infected external ear canal under direct visualization through a surgical microscope. Cotton swabs (Transwab ENT, Medical Wire & Equipment Co, Ltd, Corsham, England) were used for sampling pus and exudate, and sterile Hartmann-Wullstein ear forceps were used for obtaining granulation tissue. When pus, exudate, or granulation tissue was not present posttherapy or following reepithelialization of the external ear canal, cultures were obtained after the surface of the external ear canal was cleansed by nonbacteriostatic saline to minimize surface contamination. Bacterial and fungal strains isolated from purulent ear drainage or material obtained at time of debridement were identified according to standard laboratory techniques. Each bacterial isolate was tested for susceptibility to ofloxacin by the agar diffusion method using a commercial 5-μg ofloxacin disc (Oxoid, Basingstoke, England) as well as for susceptibility to additional antimicrobial agents commonly employed in the treatment of IEO. The break-points for ofloxacin susceptibility by the agar diffusion methods were defined according to the National Committee for Clinical Laboratory Standards. Inhibition zones of ≤12 mm were considered resistant, while inhibition zones of ≥16 mm were considered as susceptible. These break-points correspond to ofloxacin minimum inhibitory concentrations of ≥8 and ≤2 μg/mL, respectively.[13]

Clinical and Laboratory Follow-up. During therapy, the patients were followed up on a weekly basis. Each week a complete physical examination and microscopic otoscopy were performed. Cultures were obtained from debrided material and purulent discharge. Blood and urine tests were repeated. At each visit the patients were asked about potential adverse reactions to the drug. Patients were also instructed to notify the attending physician on in-between visits if their condition worsened or if they suspected that a side effect had developed. Audiometric tests were repeated upon completion of ofloxacin therapy. Repeat radiographs and Tc 99 bone scans were obtained during therapy as clinically indicated and upon completion of therapy.

Posttherapy follow-up was conducted at 1, 3, 5, 8, 16, and 24 weeks following completion of ofloxa-

RESULTS OF OFLOXACIN THERAPY

Patient No.	*Age (y)*	*Sex*	*Isolated Organisms*	*Enrollment ESR (mm/h)*	*Duration of Therapy (d)*	*Outcome*	*Follow-up (mo)*
Group A							
1	75	M	PA	60	37	C	24
2	73	F	PA	80	29 + 21	RC	20
3	70	M	PA, SE	50	28	C	12
4	43	M	PA	70	10	FS	NA
5	40	F	PA	100	30 + 27	RC	12
6	19	F	PA	60	21	C	8
7	80	M	PA	80	35	C	12
8	75	M	PA	80	28	C	28
9	77	M	PA	70	30	C	32
Group B							
10	84	M	PA, SA	120	54	C	38
11	55	M	PA	120	51	C	36
12	76	F	PA	100	54	C	30
13	70	F	PA, SA	100	65	C	28
14	80	M	PA	>120	94	C	24
15	67	M	PA, SA	100	45	C	19
16	84	M	PA	>120	85	C	18
17	51	M	PA	110	60	C	12
18	81	M	PA	120	42	C	11
19	85	M	PA	100	62	FR	NA
20	65	F	PA, PM	100	49	C	8
21	87	M	PA	120	37	C	6
22	45	M	PA	110	62	FR	NA
23	34	F	PA	100	61	FR	NA
24	64	M	PA, EC	110	65	C	7

ESR — erythrocyte sedimentation rate, PA — *Pseudomonas aeruginosa*, SE — *Staphylococcus epidermidis*, SA — *Staphylococcus aureus*, PM — *Proteus mirabilis*, EC — *Escherichia coli*, C — cure, RC — relapse and cure after second ofloxacin course, FS — failure due to severe side effects, FR — failure due to resistant pseudomonal strains, NA — not applicable.

cin therapy. On each visit an interim medical history was taken, detailed physical examination findings and otoscopic findings were recorded, and bacterial and fungal cultures were obtained. Additional tests were performed if clinically indicated.

Definition of Therapeutic Response. Cure was defined as resolution of all signs and symptoms related to the infection, a decrease in ESR toward normal values, and absence of pathogens in three consecutive cultures obtained from the affected ear. Relapse was defined as reappearance of signs and symptoms during the follow-up period after completion of ofloxacin therapy. Therapy was considered a failure if any of the following occurred: 1) insufficient lessening of signs and symptoms after 8 weeks of ofloxacin therapy, 2) evidence that the original pathogen(s) developed in vitro resistance to ofloxacin during therapy (concomitant with reappearance or lack of disappearance of symptoms), or 3) appearance of severe side effects requiring discontinuation of ofloxacin therapy.

Duration of Therapy. Ofloxacin therapy was continued until the signs and symptoms related to the infection resolved and three consecutive cultures from the involved ear canal were sterile. The end of therapy was defined as the time at which the third sterile culture was obtained.

RESULTS

Twenty-six patients were initially enrolled in the study. Two patients were excluded from the study. In one patient pathologic examination of the "granulation" tissue removed from the ear canal during debridement revealed squamous cell carcinoma, and one woman was excluded because she was found to be pregnant. There were no noncompliant patients. The clinical aspects and course of therapy of the remaining 24 patients, 17 men and 7 women, 19 to 87 years of age (mean, 65.8 years), are summarized in the Table.

Nine patients were classified as suffering from the mild form of IEO (group A) and 15 patients as suffering from the severe form (group B). *Pseudomonas aeruginosa* was isolated in all the patients prior to treatment. In 18 patients *P aeruginosa* was the only pathogen isolated and in the other 6 patients additional organisms were cultured (*Staphylococcus epidermidis, Staphylococcus aureus, Proteus mirabilis*, and *Escherichia coli*). All the isolated bacteria were sensitive to ofloxacin (see Table).

On enrollment ESR was elevated (50 to 100 mm/h) in 8 of the 9 patients of group A (in 1 patient it was 100 mm/h), and markedly elevated (≥ 100 mm/h) in all the patients of group B (see Table). Pretreatment serum glucose of the diabetic patients ranged from 160 to 300 mg/dL, and indeed, 7 of the 16 patients with diabetes mellitus required a change in the diabetic control regimen. The white blood cell count ranged from 4.1 x 10^3/mm^3 to 10.5 x 10^3/mm^3. A "left shift" in the differential count was observed in 2 patients only. All the other pretreatment hematologic and serum chemical test results were generally within normal limits.

Underlying conditions were identified in 21 patients and included diabetes mellitus (n = 16), ischemic heart disease (n = 5), hypertension (n = 4), peripheral vascular disease (n = 3), state after cerebrovascular accident (n = 3), malignant diseases (n = 3), state post irradiation therapy to the head and neck (n = 2), psoriasis (n = 1), and gout (n = 1). In 3 patients no underlying disease was observed. All the patients complained of otalgia on enrollment. Other presenting symptoms included purulent otorrhea (n = 19) and headaches (n = 10). All the patients had a unilateral infection. The tympanic membrane was intact in 21 patients. In 1 patient the eardrum was partially covered by granulation tissue, and in 2 others chronic otitis media with perforation of the eardrum was noted. In these last 2 patients IEO was regarded as secondary to pseudomonal otitis media. Cranial nerve involvement was observed in 5 patients of group B only. In all 5 patients the ipsilateral facial nerve was affected. The hypoglossal nerve was also involved in 1 of these patients and the vagal and glossopharyngeal nerves were also affected in another.

In addition to ofloxacin therapy given as described before, gentamicin and tobramycin drops were topically administered into the ear in 22 patients. Surgical treatment included debridement of granulation tissue (n = 24), removal of cartilaginous sequestra (n = 5), and mastoidectomy (n = 1).

Twenty patients (83.3%) were cured and 4 (16.7%) failed ofloxacin treatment. The mean total duration of a single ofloxacin course was 29.75 days (range, 21 to 37 days) for group A patients and 58.4 days (range, 37 to 94 days) for group B. Two patients of group A required a second course of ofloxacin treatment after relapse of the disease. In 3 (from group B) of the 4 patients failing treatment, ofloxacin therapy was discontinued owing to the emergence of *P aeruginosa* strains resistant to ofloxacin (as defined in the Patients and Methods section) on day 61 in 1 patient and on day 62 in 2 patients (see Table). These strains were also resistant to cefsulodin in 2 patients and piperacillin and gentamicin in 3 patients, but sensitive to ciprofloxacin in 2 patients, amikacin in 3 patients, and ceftazidime in 1 patient. The fourth patient (from group A) developed severe adverse reactions to the drug (rash and pruritus) and ofloxacin therapy was stopped (see Table).

Other ofloxacin-related adverse reactions included transient nausea (n = 2), vaginal itching (n = 1), and arthralgia of the knee (n = 1). These side effects were mild and ofloxacin therapy was continued. Superinfection of the diseased ear canals by *Candida albicans* by the end of ofloxacin treatment was observed in five patients. Results of audiometric evaluations (bone conduction only) performed before and by the end of ofloxacin treatment were within normal limits. No abnormal laboratory results were found during or after ofloxacin therapy.

DISCUSSION

Invasive external otitis is a disease of the external auditory canal capable of invading adjacent tissues, and it may even progress into more distant regions such as the temporal bone and the base of skull if not treated properly or owing to the causative organism and host factors. The extent of tissue invasion by the disease may influence treatment results. Therefore, in evaluating the efficacy of any treatment modality of IEO, the severity and the extent of the disease should be considered. We suggest that IEO can be divided into two forms: a severe form and a mild form capable of progressing into the severe form. In the mild form of IEO, the disease is limited to the epithelium and subepithelial stroma of the canal, and in the severe form the disease spreads to the cartilage and beyond the soft tissues of the external ear canal. In the present study, the severity of the disease was established according to Tc 99 bone scan results. Although Tc 99 bone scan has been suggested as a good means for monitoring the disease severity, the specificity of this test is low.[14] Since the ESR was <100 mm/h in eight of nine patients from group A and ≥ 100 mm/h in all group B patients, it is suggested that ESR and Tc 99 bone scan should be used to monitor the severity of the disease and differentiate between the two forms of IEO. A shorter duration of ofloxacin therapy (mean, 35.7 days) in group A patients emphasizes the milder form of IEO of this group as compared to group B (mean, 58.4 days). Moreover, ofloxacin-resistant *P aeruginosa* strains did not develop in any group A patients, whereas three patients of group B developed such strains. It is possible, however, that the emergence of ofloxacin-resistant strains was a result of the prolonged therapy duration of group B patients.

Cure was achieved in 20 of 24 patients (83.3%). The cure rate was somewhat higher in group A (8 of 9 patients or 87.5%) than in group B (12 of 15 patients or 80%). These results are different from those reported by Meyers et al,[4] who found a lower cure rate in patients treated with cefsulodin (64%) and another combination therapy (70%). However, a different definition for disease severity and the fact that only 2 patients had very extensive IEO (multiple cranial nerve involvement) may account for the better cure rate found in our study. A recent study found similar efficacy of three orally administered fluoroquinolones (ofloxacin, ciprofloxacin, and pefloxacin) in the treatment of IEO.[15] However, ciprofloxacin was given in a dose of 750 mg twice daily, while ofloxacin and pefloxacin were given as in our study (400 mg twice daily). The duration of therapy in our study was only 35.7 days (range, 21 to 57 days) in patients with the mild form of IEO, whereas the patients with the more extensive disease required 58.4 days (range, 37 to 94 days). Similar therapy periods were described in other treatment modalities for IEO.[4,7]

Considering the long treatment period needed for most of our patients, the drug was well tolerated except for minor side effects observed in some patients. Severe adverse reaction requiring discontinuation of ofloxacin therapy occurred in only one patient. Superinfection of the diseased external ear canals by *C albicans* species by the end of ofloxacin therapy was found in five patients and resolved after topical treatment. As all evaluated patients were given topical treatment with either gentamicin or tobramycin, it was not clear whether candidal superinfection observed in these patients was the result of the prolonged administration of oral ofloxacin or due to the topical treatment itself. Recurrent disease after apparent cure has occurred in two patients only, and these patients were cured after a second course of ofloxacin therapy. Since relapse has been described up to 1 year following cessation of therapy,[14] continued follow-up is required in the four patients of the present study that were followed up for less than 1 year.

Treatment failure due to emergence of resistant pseudomonal strains occurred in three patients. Since no attempts were made to serotype or biotype the isolates from these patients, it remained unclear whether the resistance developed during therapy arose by selection or was due to newly acquired resistant strains of the same species. Similar low incidences of emergence of resistance have also been reported with other quinolone derivatives in patients with gram-negative bacillary bone infection.[11]

As suggested by Rubin and Yu,[14] local application of aminoglycoside drops alone seems insufficient in the treatment of all forms of IEO. Indeed, all the patients in the present study were enrolled only after failure of topical antibiotic treatment. The role of local surgical procedures alone or combined with local antibiotic agents cannot be inferred from our study, because all the patients underwent local and systemic treatment. There is some difficulty in evaluating the role of ofloxacin in the treatment of patients suffering from the mild form of IEO, since this study was conducted as an open-label, noncomparative study and all the patients were treated locally as well as systemically. However, as all these patients failed topical treatment with aminoglycoside drops prior to enrollment into the study, it may be assumed that these patients were cured in response to concomitant local antibiotic drops and surgery and systemic ofloxacin treatment. Of the 24 evaluated patients, 1 patient underwent mastoidectomy, while the rest were treated by minor surgical procedures such as debridement of granulation tissue and removal of bony or cartilaginous sequestra from the diseased ear canals. We share the opinion expressed by other investigators[5,14] that the role of surgery in IEO should be limited to local procedures, and major operations such as subtotal temporal bone resection, facial nerve decompression, parotidectomy, and other aggressive surgical procedures advocated for this disease in the past should be abandoned. With early diagnosis and proper medical therapy the disease can be effectively controlled and cured.

CONCLUSIONS

Ofloxacin therapy has proved to be as effective as other antipseudomonal agents in the systemic treatment of IEO. Since ofloxacin is administered orally and side effects are rare and minor, patients can be treated at the outpatient clinic, thus sparing hospitalization hazards and expenses. It may be concluded that ofloxacin, and probably other fluoroquinolones, are promising new antibiotic agents that offer a relatively safe, economical, and more convenient alternative to the more expensive and often toxic conventional injection therapy for IEO.

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EXTRACRANIAL OPTIC NERVE DECOMPRESSION MEETING

An Extracranial Optic Nerve Decompression Meeting will be held Nov 2-3, 1991, in Boston. For further information, contact Michael P. Joseph, MD, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114; (617) 573-3192.

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DISTRIBUTION OF IMMUNOCOMPETENT CELLS IN NORMAL NASAL MUCOSA: COMPARISONS AMONG GERM-FREE, SPECIFIC PATHOGEN–FREE, AND CONVENTIONAL MICE

ISSEI ICHIMIYA, MD

HIDEYUKI KAWAUCHI, MD
TAKAHIRO TANAKA, MD

TATSUYA FUJIYOSHI, MD
GORO MOGI, MD

OITA, JAPAN

To better understand the role of immunocompetent cells in the defense mechanism of the upper respiratory tract against microbial invasions, the distribution patterns of those cells were investigated in nasal mucosa of mice maintained in three different conditions: germ-free (GF), specific pathogen–free (SPF), and conventional (CV) conditions. Immunostaining by the indirect peroxidase method and toluidine blue staining were employed for the detection of immunocompetent cells and mast cells. For immunostaining, anti-IgG, -IgA, and -IgM polyclonal antibodies and anti-Lyt-1, -Lyt-2, and -Mac-1 monoclonal antibodies were used as primary antibodies. In nasal mucosa of CV mice, Mac-1$^+$ cells, mast cells, and all cell types of lymphocyte subsets were present. In nasal mucosa of SPF mice, all cell types were also positive, but fewer in number than those of CV mice. In nasal mucosa of GF mice, IgG$^+$, IgA$^+$, and Lyt-2$^+$ cells were rare, although IgM$^+$ and Lyt-1$^+$ cells were present in small numbers. An electron microscopic study revealed that follicle-like lymphocyte aggregates with high endothelial venules were present in nasal mucosa close to the mucosal epithelia. These findings suggest that lymphocytes are mobilized to nasal mucosa, responding to continuous antigenic stimuli, and play an important role in the local defense mechanism of the upper respiratory tract.

KEY WORDS — germ-free condition, immunohistochemistry, mucosa-associated lymphoid tissue, nasal mucosa.

INTRODUCTION

The nasal mucosa is considered to be the first line of defense of the respiratory tract, protecting it from invading antigens. The local immunity of the nasal cavity has been well investigated, and mucosal immunity has been proven to be present in nasal mucosa as well as bronchial and intestinal mucosae.[1-6] An established immunohistochemical analysis with available monoclonal antibodies makes it possible to identify immunocompetent cells in human nasal mucosa. It has been reported that lymphocyte subsets distribute in human nasal mucosa,[1] expressing surface markers of B cells, helper/inducer T cells, and suppressor/cytotoxic T cells. However, human nasal mucosa is considered to have been circumstantially stimulated so often with miscellaneous antigens that it is impossible to examine nasal mucosa in an infection-free condition without modification of histology by antigenic exposure.

In the present study, for better understanding of the development of local immunity in the nasal cavity, we employed mice raised in three different conditions: germ-free (GF), specific pathogen–free (SPF), and conventional (CV). Mice bred in the GF condition are considered to receive much fewer antigenic stimuli than CV and SPF mice. Therefore, a comparative study of the distribution patterns of immunocompetent cells among these mice was useful for the evaluation of the local immune system of the nasal mucosa. Moreover, in this study, the fine structure of lymphocyte aggregate was demonstrated in nasal mucosa, which resembles mucosa-associated lymphoid tissue (MALT).

MATERIALS AND METHODS

Animals. Strain ICR male mice 6 to 8 weeks old were used for the experiments. A total of 15 ICR mice (5 each) were purchased in GF, SPF, or CV conditions from a local breeder (Seiwa Institute for Experimental Animals, Fukuoka, Japan). Every mouse in each group was confirmed macroscopically to be free of nasal diseases before they were painlessly killed.

Tissue Processing. The skulls of the animals were dissected and nasal mucosae were removed with the facial bones. Nasal mucosae were immediately fixed with periodate-lysine-paraformaldehyde[7] for 12 hours at 4°C, then decalcified with 10% ethylenediaminetetraacetic acid in 0.1 mol/L Tris buffer (pH 6.95) for 5 days at 4°C, washed with 0.01 mol/L phosphate-buffered saline (PBS, pH 7.2) containing 10% to 20% sucrose for 24 hours at 4°C, and embedded in OCT compound (Miles Laboratories, Naperville, Ill). Embedded tissues were immediately frozen and stored until use.

Immunohistochemical Investigations. Specimens were serially sectioned at a 6-μm thickness vertically to the long axis of the nasal cavity and air-dried at room temperature. The serial sections were stained by an indirect immunoperoxidase method. The following antibodies were employed: rabbit anti

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From the Department of Otolaryngology, Medical College of Oita, Oita, Japan.

REPRINTS — Goro Mogi, MD, Dept of Otolaryngology, Medical College of Oita, 1-1, Idaigaoka, Hazama-cho, Oita 879-56, Japan.

TABLE 1. ANTIBODIES USED IN EXAMINATION OF NASAL MUCOSA

Antibodies	*Cell Specificity*
Polyclonal antibodies	
To murine IgG	
To murine IgA	
To murine IgM	
Monoclonal antibodies	
To Lyt-1	Differentiated T cells (including helper T cells, delayed hypersensitivity T cells)
To Lyt-2	Suppressor T cells, cytotoxic T cells
To Mac-1	Monocytes, granulocytes, natural killer cells

mouse IgG (1:200, Zymed Laboratories, San Francisco, Calif), rabbit anti mouse IgA (1:200, Zymed), rabbit anti mouse IgM (1:200, Zymed), rat anti–Lyt-1 (1:100, Becton Dickinson Immunocytometry Systems, Mountain View, Calif), rat anti–Lyt-2 (1:20, Becton Dickinson), and rat anti–Mac-1 (1:20, Hybritech, San Diego, Calif). Table 1 lists the antibodies used in this study.

After rehydration of the tissues on the slide with PBS, serial sections were incubated at room temperature for 60 minutes with the series of primary antibodies. Following incubation with those antibodies, the sections were sequentially incubated for 60 minutes with peroxidase-conjugated goat anti rabbit IgG (1:50, Cooper Biomedical, Malvern, Pa) or goat anti rat IgG (1:200, Cooper), both containing 2% murine serum. Between steps, the sections were washed in three changes (10 minutes each) with PBS. The reaction product was developed with 0.02% 3,3′-diaminobenzidine in 0.05 mol/L Tris buffer (pH 7.6) with 0.005% hydrogen peroxide for 7 minutes. Sections were counterstained with veronal acetate–buffered 1% methyl green solution, dehydrated, cleared in xylol, and mounted.

Control stainings for specificity of antibodies performed with PBS instead of primary antibodies all proved negative. The reactivity of antibodies was examined in frozen sections of lymph node, spleen, and Peyer's patch.

Also, adjacent serial sections were stained with toluidine blue for the detection of mast cells, and with hematoxylin and eosin for the observation of histopathologic details.

Three-dimensional Reconstruction of Nasal Mucosa. In order to visualize the location of lymphocyte aggregates, three-dimensional images of the nasal cavity were reconstructed with a computer. Photographs of serial sections were digitized by a graphic digitizer (Nexus 68230, Kashiwagi Research Co, Tokyo, Japan), and x and y coordinate data for reconstruction were entered into a computer system (Sun 4/110, Sun Microsystems, Mountain View, Calif) with an image processor (Nexus 6800, Kashiwagi). The software for three-dimensional reconstruction was purchased from Ratoc System Engineering Co (Tokyo, Japan).

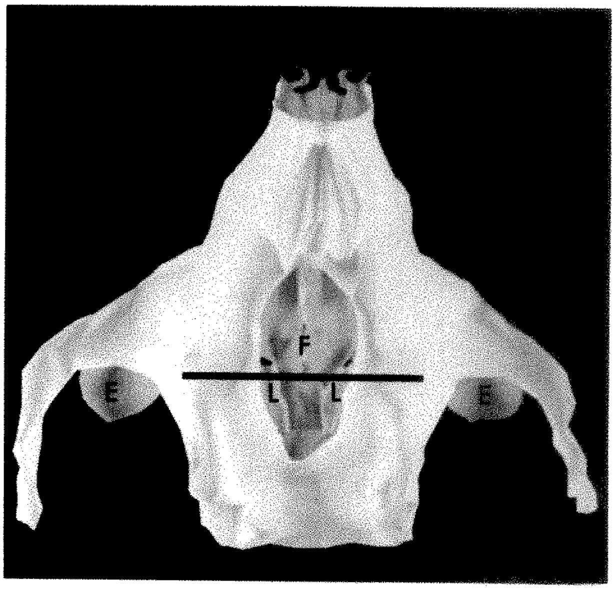

Fig 1. Three-dimensional reconstruction image of skull showing dorsal view. Line represents cross portion for cell countings. Lymphocyte aggregates (L) are seen on floor of nasal cavity at incisive foramen (F). E — eyeball.

Histologic Evaluation. Positive cells in nasal mucosa that were stained by the immunoperoxidase technique were observed by light microscopy at both x100 and x400 magnifications. For quantitative analysis, cell counting was done in each specimen at the same portion of the nasal cavity. The portion was the coronal section at about the anterior one third of the nasal cavity, crossing the incisive foramen, as shown in Fig 1. Cell counting was carried out by two authors (I.I. and H.K.) and double-checked. The length of the mucosa in which positive cells were counted was measured by the Nexus 6800, and positive cell numbers per square millimeter of surface area of the mucosa were calculated as described in a previous report.[8]

Statistical Analysis. Because of the skewed distribution of positive cell numbers, the median and ranges of cell numbers were calculated. Statistical analysis was done by the Wilcoxon rank sum test or the Kruskal-Wallis H test.

RESULTS

In the nasal mucosa of all mice bred in GF, SPF, and CV conditions, lymphocytes were dominant, although neutrophils and macrophages were also seen. However, the numbers of lymphocyte subsets were different among the three conditions (Table 2). The differences are described respectively, as follows.

Germ-free Mice. A small number of lymphocytes, Mac-1–positive (Mac-1$^+$) cells, and mast cells were seen in the nasal mucosa of GF mice. Lymphocytes aggregated in the mucosa on the floor of the nasal cavity, but did not scatter in the mucosa. The ratio

TABLE 2. DISTRIBUTION OF CELLS IN NASAL MUCOSA

	GF	*SPF*	*CV*
IgG*	0.0 (0.0- 0.0)	16.6 (0.0- 70.8)	721.7 (237.7- 868.6)
IgA*	0.0 (0.0- 0.0)	73.8 (35.9- 118.0)	399.3 (160.0- 502.2)
IgM	45.5 (0.0-121.9)	27.9 (17.5- 88.6)	127.6 (13.1- 418.9)
Lyt-1*	108.1 (0.0-185.7)	400.0 (73.4-1,070.0)	1,749.8 (1,006.1-2,043.0)
Lyt-2*	0.0 (0.0- 23.0)	53.1 (21.7- 554.2)	640.8 (277.8-1,263.5)
Mac-1*	30.9 (0.0- 42.1)	70.7 (7.1- 149.0)	442.9 (266.2- 569.0)
Mast†	42.8 (22.9-136.2)	28.1 (16.6- 136.2)	252.5 (97.7- 320.9)

Data are cells/mm^2, median (range); n = 5 for each sample tested.

GF — germ-free condition, SPF — specific pathogen-free condition, CV — conventional condition.

*CV > GF, $p < .05$ (Wilcoxon test), and CV > SPF > GF, $p < .005$ (Kruskal-Wallis H test).

†CV > GF, $p < .05$ (Wilcoxon test).

of lymphocytes, Mac-1$^+$ cells, and mast cells was about 3 to 0.7 to 1.

As for the lymphocyte subset, only IgM$^+$ cells and Lyt-1$^+$ cells were seen, and the median numbers of these cells were 45.5/mm^2 and 108.1/mm^2. Neither IgG$^+$ cells nor IgA$^+$ cells were seen. A small number of Lyt-2 cells was seen in two animals out of five, which was exceptional.

Specific Pathogen-Free Mice. In the nasal mucosa of SPF mice, inflammatory cells were higher in number than in the nasal mucosa of GF mice. The ratio of lymphocytes, Mac-1$^+$ cells, and mast cells was 20 to 2.5 to 1. Lymphocyte aggregates were also seen in the mucosa on the floor of the nasal cavity, and a small number of lymphocytes scattered in the mucosa.

The SPF mice had all types of lymphocyte subsets in the nasal mucosa. Lyt-1$^+$ cells, which represented 400/mm^2, also were the majority among lymphocyte subsets, but the number of IgM$^+$ cells was fewer than that of IgA$^+$ cells (IgM$^+$ cells, 27.9/mm^2; IgA$^+$ cells, 73.8/mm^2).

Conventional Mice. Among the three groups, the total number of inflammatory cells in the nasal mucosa was the highest in the CV mice. The ratio of lymphocytes, Mac-1$^+$ cells, and mast cells was 14 to 8 to 1. Lymphocyte aggregates were also seen, and their size was the largest among the three groups (Fig 2). Lymphocytes scattered in the mucosa, but most of those cells distributed near the aggregates.

All types of lymphocyte subsets were seen in the nasal mucosa of CV mice. In particular, Lyt-1$^+$ cells (Fig 3A) had a majority, showing 1,749.8/mm^2 in number. Characteristics of the CV mice were that IgG$^+$ cells (Fig 3B) and Lyt-2$^+$ cells were seen in large numbers (721.7/mm^2 and 640.8/mm^2). The ratio of Lyt-1$^+$ cells to Lyt-2$^+$ cells was 2.7 to 1.

The lymphocyte aggregates consisted of zones of Lyt-1$^+$ cells, and high endothelial venules were identified as well.

Three-dimensional Reconstruction Images. Sites of lymphocyte aggregates in the nasal mucosa were visualized by three-dimensional reconstruction images. In all mice, lymphocyte aggregates were observed at the same place, which was at the edge of the incisive foramen, ie, a single oval slit at the junction of the incisive and maxillary bones. They were observable through this foramen, from the dorsal view of the skull (Fig 1).

DISCUSSION

In the present study, the distribution of immunocompetent cells in the nasal mucosa was examined in order to investigate the local immune system of nasal mucosa. As regards B cell subsets, IgG$^+$ cells, IgA$^+$ cells, and IgM$^+$ cells were observed in that order of frequency in the nasal mucosa of CV mice,

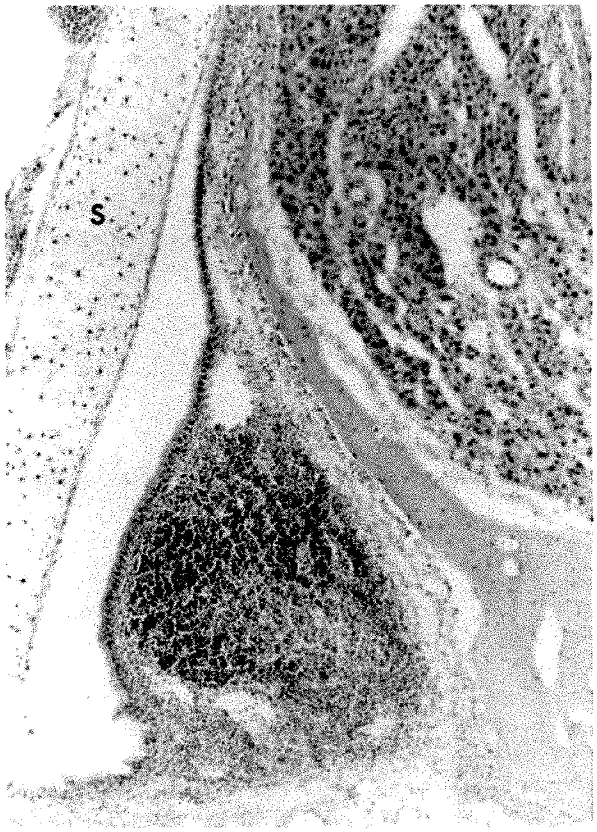

Fig 2. Light micrograph of nasal mucosa of conventional mouse showing lymphocyte aggregate, which is in close contact with mucosal epithelium (H & E, original x50). S — nasal septum.

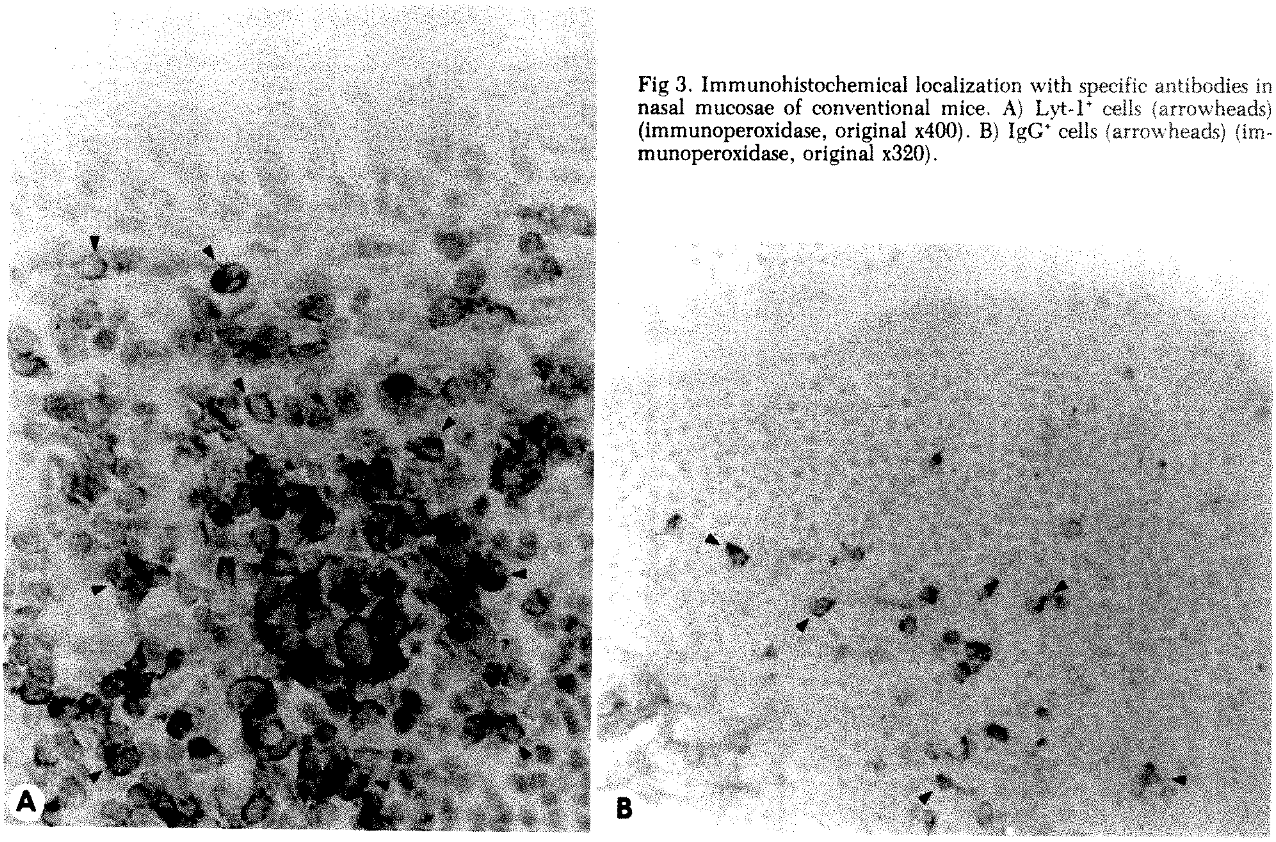

Fig 3. Immunohistochemical localization with specific antibodies in nasal mucosae of conventional mice. A) Lyt-1⁺ cells (arrowheads) (immunoperoxidase, original x400). B) IgG⁺ cells (arrowheads) (immunoperoxidase, original x320).

as shown in Results. As regards T cell subsets, Lyt-1⁺ cells were seen in higher numbers than Lyt-2⁺ cells. These findings correspond with studies of lymphocyte subsets in nasal mucosa biopsy specimens of healthy humans.[1]

Our data showed that there were fewer immunocompetent cells in GF mice than in SPF and CV mice. This result suggests that immunocompetent cells distributed in normal nasal mucosa might locally develop or mobilize from systemic circulation according to antigenic stimuli. Moreover, differences in the ratio of lymphocyte subsets among nasal mucosa of GF, SPF, and CV mice indicate that the immune condition changes according to the stimuli.

Germ-free mice have been found to be unique in immunologic characteristics, not only because they are infection-free animals, but because they lack bacterial flora.[9] It has been reported that Peyer's patches in GF animals were smaller, and that the small intestines of SPF and CV mice synthesized IgA in spite of the fact that no immunoglobulin synthesis was detectable in the GF condition.[10] In another study,[11] only IgM was synthesized by lymphoid cells from spleen, lymph nodes, and thoracic ducts of GF mice, whereas cells from CV mice also synthesized IgG. From these results, it is believed that animals in the GF condition are immunologically immature because they are rarely exposed to antigenic stimuli. Murine nasal mucosa in the GF condition, which was proven to possess no IgG⁺ cells or IgA⁺ cells, can be considered to be immunologically immature for the lack of antigenic stimuli from inhaled air. Absence of Lyt-2⁺ cells in the nasal mucosa of GF mice might also suggest the immaturity of the cell-mediated immune response in that condition.

Follicle-like lymphocyte aggregates were observed in the nasal mucosa of every mouse raised in various conditions, with a different size among the three groups. Presence of lymphocyte aggregates in normal nasal mucosa was previously demonstrated in primates (ie, tree shrews, slow lorises, and monkeys)[12]; however, the function of these lymphocytes has not been investigated. In the present study, IgG⁺ cells and IgA⁺ cells tended to distribute in and around the follicle-like lymphocyte aggregates. This finding suggests the possibility that immunoglobulin-forming cells in the nasal mucosa are differentiated locally from the lymphocyte aggregates. From a morphologic standpoint, lymphocyte aggregates in nasal mucosa are somewhat like bronchus-associated lymphoid tissues (BALTs) and gut-associated lymphoid tissues (GALTs).[13-16] High endothelial venules, which are a characteristic in BALTs and GALTs, as well as lymph nodes, were also present in the lymphocyte aggregates of the nasal mucosa. Lymphocytes are located between high endothelial cells and pericytes, or in the lumen of a venule. These findings indicate that lymphocytes may migrate across the endothelial layer to contribute to the local immunity of the nasal mucosa.

Moreover, electron microscopic observation (data not shown) revealed nonciliated cells among the dominant ciliated cells of the mucosal epithelium of the nose, where lymphocyte aggregates were seen. Findings of these nonciliated cells were similar to those of microfold cells in BALTs and GALTs. This suggests that the epithelium might be a site for initiation of the immune response in the nasal cavity.

In summary, the present study compared the distribution patterns of immunocompetent cells in murine nasal mucosae raised in various conditions. Nasal mucosa is believed to mature in its local immunocompetence by repeated contact with environmental antigenic stimuli. Although a lymphocyte aggregate was observed, further functional studies are needed to understand whether this aggregate can be considered to be MALT.

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APRON TRACHEOSTOME

MOHAMMAD TALAAT, MCH

ALEXANDRIA, EGYPT

Stenosis of the tracheostome following total laryngectomy is not an infrequent complication, either immediately postoperatively or years later, and it poses a common problem for head and neck surgeons. The opening becomes inadequate and the patient is uncomfortable and panicky. A secondary plastic operation is necessary in order to improve the airway, or a laryngectomy tube must be worn constantly. I have developed a satisfactory technique for tailoring the tracheostome during total laryngectomy so as to minimize postoperative stenosis even in irradiated cases and allow the patient to dispense with the laryngectomy tube. It may render the posterosuperior wall of the tracheostome more suitable for a tracheoesophageal puncture tract for voice restoration after total laryngectomy. These goals are achieved by interdigitating a small skin-thick superiorly based apron flap, raised from the lower midline of the front of the neck, into a similar recipient area at the upper posterior tracheal wall after removal of an equal mucosal apron.

KEY WORDS — laryngectomy, skin flaps, tracheostomy.

SURGICAL TECHNIQUE

Skin Incisions and Flaps. The author's technique of total laryngectomy (Fig 1) utilizes two skin incisions. One is a horizontal laryngectomy incision that is midcervical and made in a skin crease near the lower border of the thyroid cartilage. It extends between the sternocleidomastoid muscles. This incision is carried down to the strap muscles. Upper and lower skin flaps are raised in the subcutaneous plane. The second is the U-shaped tracheostomal incision, which is centered about the midline about one finger's breadth above the suprasternal notch. Its dimensions are about 2.5 x 2 cm (a little wider and longer than the cut end of the trachea). This incision is carried down to, but not including, the subcutaneous fat. It borders a superiorly based thin skin apron flap that will be raised in the subdermal plane. Subdermal infiltration with lidocaine-epinephrine using a hypodermic needle facilitates this step.

If the larynx is to be removed through a Sorensen's incision (Fig 1), the lower end of this incision is

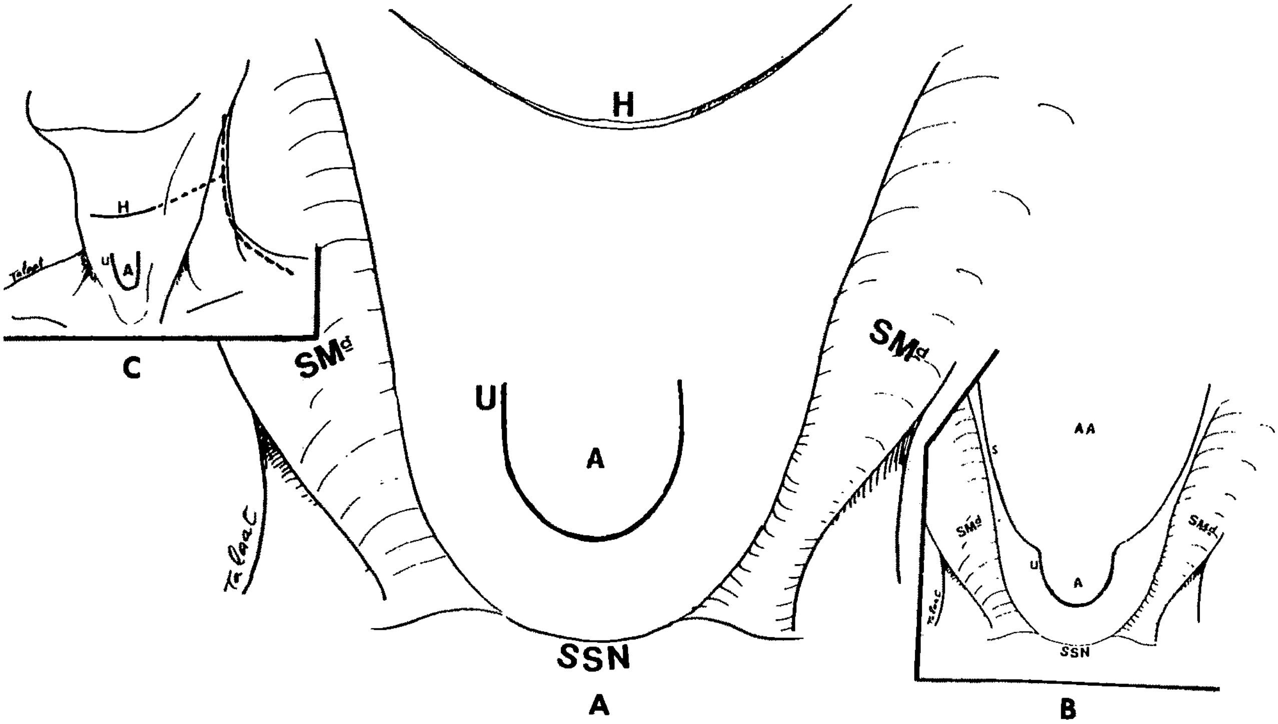

Fig 1. Skin incisions and flaps. A) Author's technique. H — horizontal laryngectomy incision, U — U-shaped tracheostome incision, A — tracheostome apron flap, SM^d — sternocleidomastoid muscle, SSN — suprasternal notch. B) Removal of larynx through Sorensen's incision (S). AA — large laryngectomy apron flap, A — daughter apron flap of tracheostome. C) Total laryngectomy with simultaneous neck dissection.

From the Department of Otolaryngology–Head and Neck Surgery, Alexandria Medical School, Alexandria, Egypt.

Presented at the Alexandria International Conference on Laryngeal Cancer, Alexandria, Egypt, April 1-2, 1987.

REPRINTS — Mohammad Talaat, MCh, Dept of Otolaryngology–Head and Neck Surgery, Alexandria Medical School, Alexandria, Egypt.

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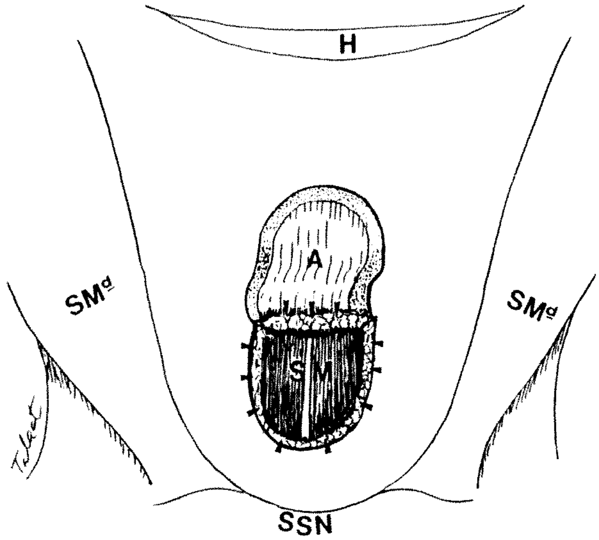

Fig 2. Raising of tracheostomal apron flap (A). Dotted area shows peripheral part of tracheostomal apron flap to be excised. Subcutaneous tissues deep to flap are excised, leaving small rim (arrowheads) and exposing strap muscles (SM). Other abbreviations as in Fig 1.

modified to be continuous with the previously mentioned U-shaped tracheostomal incision. A large laryngectomy apron flap is raised in the subcutaneous plane, while a small tracheostomal apron flap is raised in the subdermal plane. If total laryngectomy is to be done with simultaneous neck dissection, the horizontal incision is extended as shown by the dotted lines in Fig 1.

Dissection Deep to Raised Apron Flap. The disc of subcutaneous fat deep to the small tracheostomal apron flap will be excised to leave a small rim (Fig 2) that will be used later for tracheal anchorage. The strap muscles are now exposed. The peripheral strip of the small flap is excised so that the rest of the flap may rest more comfortably in its bed in the posterior tracheal wall.

Removal of Larynx. The larynx is removed from below upward as usual, but I stress the following.

1. Care should be taken while cutting the posterior tracheal muscle. A clean cut end of the muscle is important for tracheal anchorage later.
2. Submucous resection of the second or third tracheal ring will offer the cuff of mucosa necessary for perfect mucocutaneous closure.
3. The upper 2 cm of the trachea is dissected all around to facilitate tracheal exteriorization through the tracheostome and its anchorage.

Preparation of Bed for Small Flap in Posterior Tracheal Wall. A tongue equal to the small tracheostomal flap is excised from the posterior tracheal mucosa, exposing the posterior tracheal muscle (Fig 3). This mucosa-deficient area will be the bed for the flap. Submucous infiltration with lidocaine-epinephrine will facilitate this step.

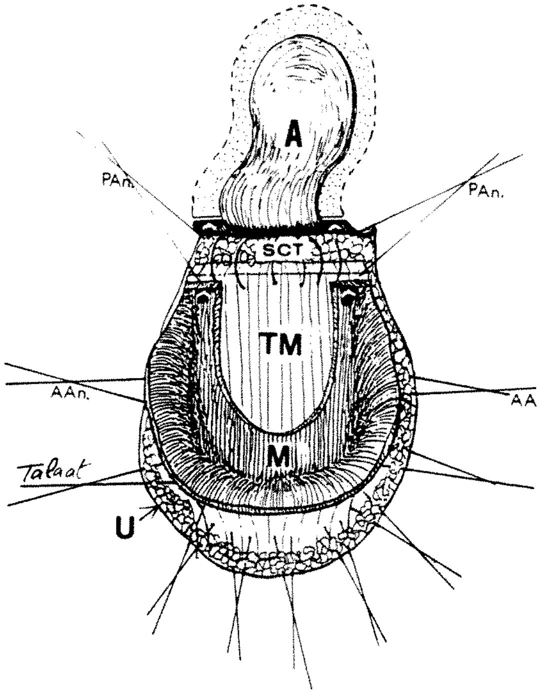

Fig 3. Preparation of bed for tracheostomal apron flap (A) and tracheal anchorage. "Tongue" equal to A is excised from posterior tracheal mucosa (M), exposing posterior tracheal muscle (TM). PAn — posterior anchoring sutures between rim of subcutaneous tissues (SCT) at base of A and upper cut edge of TM, AAn — anterior anchoring sutures between rim of subcutaneous tissues deep to U-shaped tracheostome incision (U) and peritracheal tissue.

Tracheal Anchorage. I consider this an important step. It is effected by two sets of 3-0 Vicryl sutures (Fig 3). Posterior anchoring sutures are used between the upper cut end of the tracheal muscle and the subcutaneous fat at the base of the small tracheostomal flap. Anterior anchoring sutures are used between the rim of subcutaneous fat at the U-shaped tracheostomal incision and the peritracheal tissue.

The anchoring sutures render the wound airtight and watertight and thus fulfill the following goals: septic secretions will not find their way to the depth,

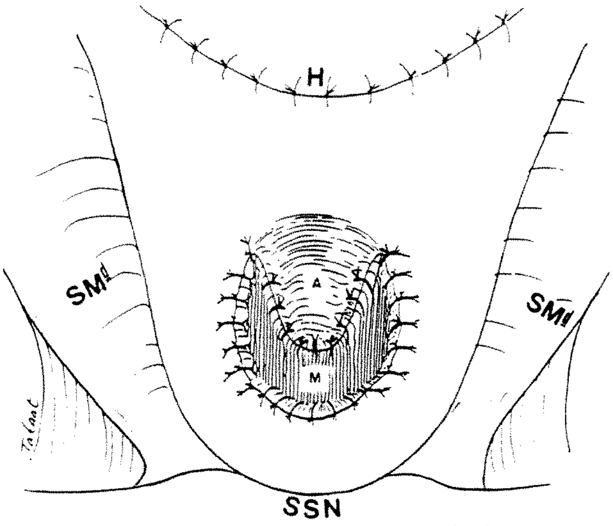

Fig 4. Wound closure. M — posterior tracheal mucosa. Other abbreviations as in Fig 1.

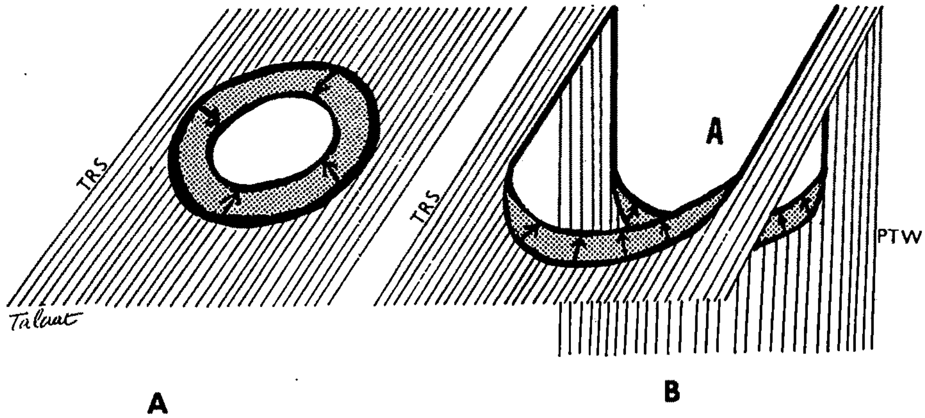

Fig 5. Planes of mucocutaneous scar. A) In ordinary permanent tracheostome, mucocutaneous scar is circle in tracheostomal plane (TRS). It completely borders tracheostome. B) In apron tracheostome (A), mucocutaneous scar is in two planes: TRS and plane of posterior tracheal wall (PTW). Scar partially borders stoma, being deficient posteriorly. Arrows — direction of scar contraction, dotted areas — extent of scar contraction.

suction drainage will be more efficient, and tracheal separation is less likely.

Wound Closure. The tracheostomal mucocutaneous closure is done with interrupted 4-0 silk sutures (Fig 4). The posterior mucocutaneous sutures fix the margin of the small tracheostomal flap to the posterior tracheal mucosa at the margin of the bare area. The anterior sutures fix the anterior tracheal mucosa to the neck skin. The laryngectomy incision is closed in layers and the wound is suction-drained.

DISCUSSION

Characteristics of Ordinary Permanent Tracheostome. The tracheostome is entirely bordered by the mucocutaneous scar. It is a well-recognized principle of plastic surgery that a circumferential scar contracts toward the center, resulting in variable degrees of stenosis of the lumen (Fig 5).

Repair of the posterior part of the tracheostome is effected by only one row of mucocutaneous stitches, as shown in Fig 6. Extension of the neck in the postoperative period may pull on these stitches.

The posterior part of the tracheostome is formed by the upper tracheal mucosa (Fig 6), which might have been compromised by irradiation of the adjacent laryngeal cancer with the possibility of breakdown. This, together with the above-mentioned pull on the posterior mucocutaneous stitches during neck extension, may help fistulization to occur in that site, with subsequent fibrosis and stenosis of the tracheostome.

Advantages of Apron Tracheostome Over Ordinary One. One advantage is that the tracheostome is wide from the start (Fig 7), since the U-shaped incision is longer and wider than the upper cut end of the trachea. There is less tendency for stenosis, because the tracheostome is partially bordered by the mucocutaneous scar, which is deficient posteriorly. The scar, therefore, is not a complete circle (Fig 5). There is less tendency for fistulization at the upper posterior part of the tracheostome for the following reasons.

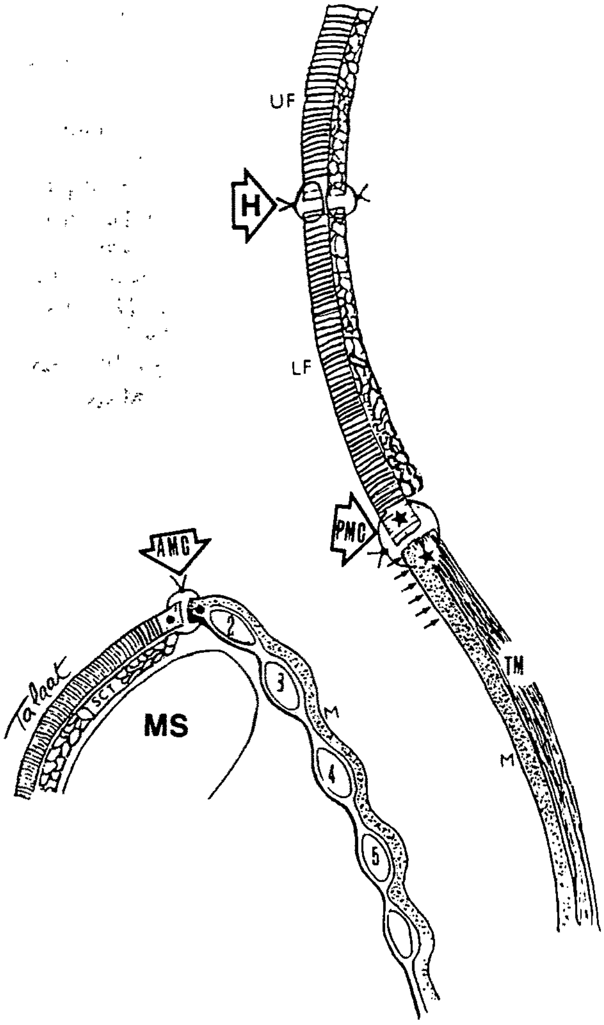

Fig 6. Ordinary tracheostome (sagittal). Upper end of trachea is fixed by only one type of suture, ie, mucocutaneous sutures. AMC — anterior mucocutaneous sutures between anterior tracheal mucosa and sternal skin, PMC — posterior mucocutaneous sutures between upper end of posterior tracheal wall and skin of neck, H — horizontal laryngectomy incision, UF — upper skin flap, LF — lower skin flap, M — tracheal mucosa, MS — manubrium sterni, TM — posterior tracheal muscle, small arrows — upper posterior tracheal mucosa that may be compromised by irradiation, 2,3,4,5 — tracheal rings (ring 1 was taken with specimen).

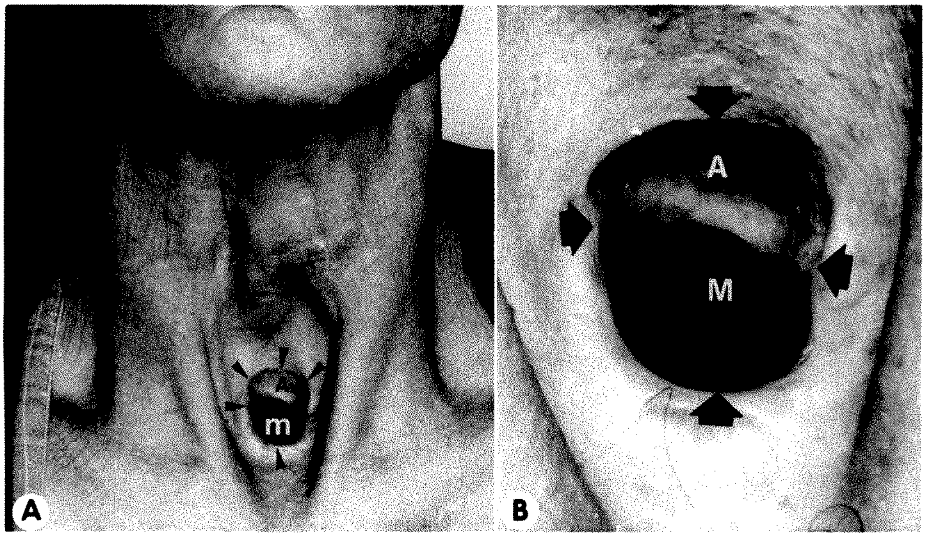

Fig 7. Photographs of patient. A — skin apron flap in upper posterior trachea, M — tracheal mucosa. A) Arrowheads mark wide apron tracheostome 2 years postoperatively. Patient does not use tube. B) Closer view of tracheostome.

Repair of the posterior part of the tracheostome is effected in two rows of stitches at two different levels and planes; the horizontal posterior anchoring suture line (Figs 3 and 8) is in a deeper plane and a higher level than the curved posterior mucocutaneous suture line (Figs 4 and 8). Extension of the neck in the postoperative period results in traction forces distributed mainly on the posterior anchoring sutures and partly on the posterior mucocutaneous sutures. Therefore, the traction forces are less effective as a cause of wound gaping and fistulization.

The airtight and watertight tracheostomal repair eliminates the spread of infection to the deeper tissues and thus there is less tendency for fistulization.

In irradiated cases, especially with high-energy beams produced by a linear accelerator and cobalt 60, the dose absorbed at the depth will become higher, with a skin-sparing effect. This means that the skin apron in its new place in the upper posterior trachea is more viable than the excised mucosal tongue, which might have been compromised by irradiation. The tendency for fistulization, therefore, will be lower.

The upper posterior part of the tracheostome is the part most subjected to mechanical trauma by air, tube, suction, etc. The skin apron in this place is definitely tougher than mucosa in withstanding these mechanical forces, and there is less tendency for fistulization.

The skin apron in the upper posterior part of the tracheostome may be more suitable than the mucosa for making a tracheoesophageal puncture tract for voice restoration after total laryngectomy.

Contraindications. Contraindications to this technique include previous tracheostomy and T4 laryngeal cancer invading the neck skin.

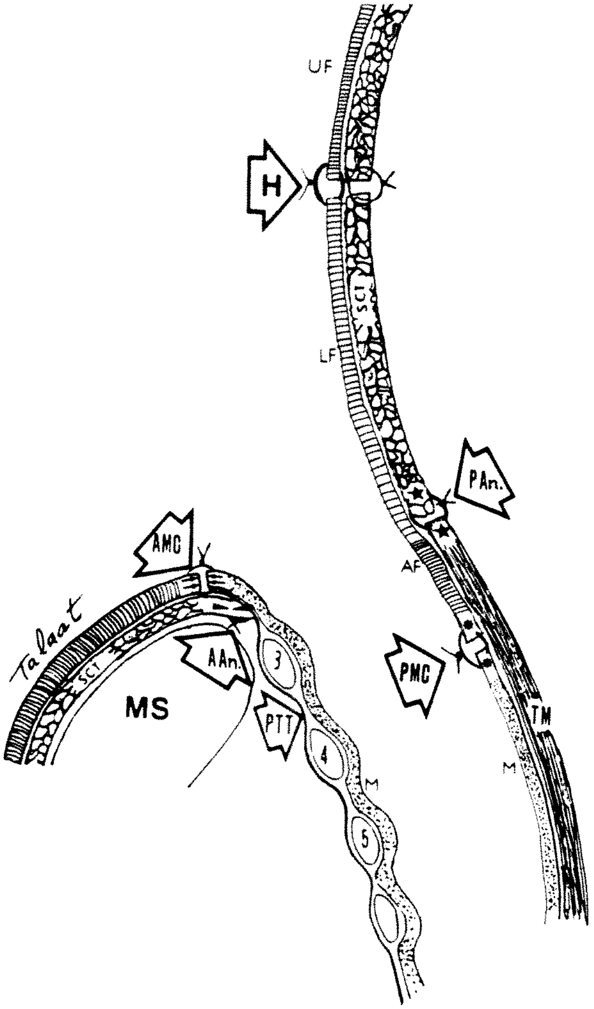

Fig 8. Apron tracheostome (sagittal). Upper end of trachea is repaired by two types of sutures: anchoring sutures and mucocutaneous sutures. PAn — posterior anchoring sutures, AAn — anterior anchoring sutures, PMC — posterior mucocutaneous sutures, AMC — anterior mucocutaneous sutures, AF — apron flap, SCT — subcutaneous tissues, PTT — peritracheal tissue, 3,4,5 — tracheal rings (ring 1 was taken with specimen and ring 2 was submucosally resected, leaving mucosal cuff). Other abbreviations as in Fig 6.

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ZINC IN THE MANAGEMENT OF TINNITUS

PLACEBO-CONTROLLED TRIAL

PETER B. PAASKE, MD
CHRISTIAN BRAHE PEDERSEN, MD
GUNNAR KJEMS
IAN LAW KUNG SAM
AARHUS, DENMARK

To assess any possible beneficial effect from zinc on tinnitus we performed a placebo-controlled, randomized, double-blind investigation. Forty-eight patients with tinnitus were randomized to either placebo or the administration of zinc sulfate as sustained-release tablets of 22 mg Zn^{++} (Zinklet). The tablets were administered three times daily for 8 weeks. Every week the patients stated the severity of tinnitus on a number scale from 0 to 10. The levels of zinc and albumin in serum were determined both before and after treatment. Of 48 patients with tinnitus, hypozincemia was found in only one patient. The zinc level increased significantly in the patients treated with zinc. We could not demonstrate any beneficial effect from zinc on tinnitus. One of the essential reasons for this finding could be that the zinc levels in serum were in the normal range previous to treatment.

KEY WORDS — tinnitus, zinc.

INTRODUCTION

The importance of zinc for the human organism was demonstrated in 1961 by Prasad et al.[1] Investigations on guinea pigs have shown a high content of zinc in the inner ear.[2] This finding has given occasion to some speculation on the role of zinc in inner ear function.

A correlation between hypozincemia and tinnitus has been reported.[3] In an uncontrolled trial by Gersdorff et al[4] zinc was found to reduce tinnitus. Shambaugh[5] found an improvement in tinnitus in 25% of patients with tinnitus and hypozincemia. The purpose of our investigation, arranged as a double-blind, randomized, placebo-controlled trial, was to study any possible beneficial effect from zinc on tinnitus.

EXAMINATIONS

Fifty patients initially participated in the investigation. All 50 previously or currently were admitted to the audiology department, Aarhus University Hospital, because of tinnitus. They all suffered from tinnitus to such a degree that they wanted some form of treatment. Later, 2 patients were excluded because they did not complete the treatment. The material, therefore, consisted of 48 patients: 31 men (65%) and 17 women (35%). The median and range of age appear in Table 1. For every patient only one ear was assessed in the investigation. In bilateral tinnitus the effect on treatment was assessed in the ear with the worse tinnitus. The duration of tinnitus and any psychosocial inconveniences were noted.

A typical otologic and audiologic examination was carried out. Pure tone audiometry was performed with a Madsen audiometer (OB 802) in a soundproof box. The thresholds of air conduction and bone conduction including the speech reception threshold were measured in decibels hearing level. The speech discrimination loss was measured in percent. The threshold of the stapedial reflex was measured by contralateral stimulation. The frequency of tinnitus was measured in the same way.

To evaluate the tinnitus and possibly contemporary hearing loss or vertigo, the patients were examined by brain stem auditory evoked potentials, calorimetric measurement by the Hallpike method, computed tomography, and ophthalmologic and neurologic tests.

A blood sample (in the morning before eating or drinking) was taken to determine the level of zinc and albumin in serum, as zinc is bound to albumin.

The test tablets were administered three times daily for 8 weeks. The tablets were randomized and contained either placebo or 100 mg zinc sulfate (22 mg Zn^{++}) as sustained-release tablets (Zinklet).

To assess a possible change in the loudness of tinnitus we chose to let the patient's own assessment be the baseline. For that purpose a numeric scale from 0 to 10 was used. Zero signified no tinnitus and 10 a severe and unbearable tinnitus. The strength of tinnitus was entered on the numeric scale before treatment began. Every week until the treatment ceased the patients used the scale to state the strength of tinnitus for the previous week.

TABLE 1. DISTRIBUTION OF PATIENTS ACCORDING TO AGE IN TWO TREATMENT GROUPS

	Zinc	*Placebo*	*Total*
Number	23	25	48
Median age	60	48	57
Age range	33-76	29-77	29-77

From the Audiological and ENT Department, University Hospital of Aarhus, Aarhus, Denmark.

REPRINTS — Peter B. Paaske, MD, ENT Dept, University Hospital of Aarhus, DK-8000 Aarhus C, Denmark.

TABLE 2. DIAGNOSIS FROM AUDIOMETRY IN 48 PATIENTS WITH TINNITUS

Cause	*No.*
Sensorineural hearing loss of unknown cause (2 patients with sudden deafness)	20
Noise-induced hearing loss	8
Noncongenital, hereditary sensorineural hearing loss	6
Sequelae to chronic otitis media	3
Tinnitus without hearing loss	3
Others (presbyacusis, temporal bone fracture, etc)	8

The effect was assessed at the end of treatment. Every score lesser or greater than before treatment that had persisted for at least a fortnight at the end of treatment was interpreted as an improvement or impairment in tinnitus, respectively. In all other cases the results were assessed as unchanged.

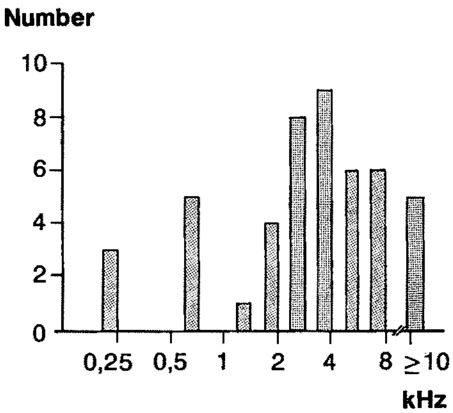
After cessation of treatment a new blood sample was taken to measure the level of zinc and albumin in serum. The zinc level was determined in undiluted serum by flame atomic absorption spectrophotometry with use of a matrix-matched (12% glycerol) standard curve.[6] Normal values of zinc range from 10 to 19 μmol/L.

The Wilcoxon rank sum test and Fisher's exact test were used in the statistical calculations. To analyze any correlation between zinc and albumin in serum the Spearman rank correlation test was applied. A significance level of 5% was chosen.

RESULTS

The duration of tinnitus varied from 3 months to 34 years (median, 5 years). Three of the patients had suffered from tinnitus less than 6 months. In 11 patients (23%) the tinnitus was present in the right ear, in 20 (42%) in the left ear, and in 16 patients (33%) in both ears. In 1 patient (2%) the tinnitus was described as central.

Forty-two patients (88%) suffered from constant and 6 patients (12%) from an intermittent tinnitus. Twenty-one patients (44%) experienced tinnitus as a high-frequency sound, 24 (50%) experienced it as a low-frequency sound, and 2 (4%) experienced both kinds of sounds. One patient (2%) experienced a pulsating tinnitus. A total of 32 patients (67%) suffered from psychosocial difficulties: 16 patients had difficulty in concentrating, 8 had difficulty in falling asleep, and 19 patients sometimes had difficulty in discriminating speech. From audiometry the diagnoses were made as shown in Table 2.



Frequency of tinnitus (measured in kilohertz) in 47 patients

TABLE 3. ZINC LEVEL IN SERUM BEFORE AND AFTER TREATMENT IN TWO GROUPS

	Before	*After*	*Difference**
Zinc group			
Median	13.3	15.4	2.3
Range	8.0-17.2	11.3-29.9	−0.5-16.0
Placebo group			
Median	12.5	12.9	0.0
Range	10.5-17.7	10.2-15.3	−5.3- 2.5

Values are μmol/L.

*Calculated on basis of individual values.

The determinations of the frequency of tinnitus appear in the Figure. The frequency was measured as pure tones in 26 patients and as narrow bands in 21 patients. In one case tinnitus was determined as white noise.

The distribution of the patients in the two different treatment groups appears in Table 1. No significant difference in age between the two groups was found.

The zinc levels appear in Table 3. In the zinc-treated group the zinc level increased significantly ($p<.01$), whereas the zinc level was unchanged in the placebo group.

The albumin levels appear in Table 4. No correlation between zinc and albumin in serum was found; hence, a rise in zinc could not be attributed to an increase in albumin. Only one zinc value was below the normal range; this was in a patient before treatment. Four zinc values were above the normal range, all among patients who had received zinc.

In both treatment groups two patients had an improvement in tinnitus. Two patients in the zinc-treated group and five patients in the placebo group had a deterioration. All other patients experienced no change in tinnitus. There was no significant difference between the results in the two groups ($p=1$). The risk of a type 2 error was 2.1%.

One patient stopped the treatment by herself 6

TABLE 4. ALBUMIN LEVEL IN SERUM BEFORE AND AFTER TREATMENT IN TWO GROUPS

	Before	*After*	*Difference**
Zinc group			
Median	38.6	36.8	−0.85
Range	33.1-43.0	33.2-43.1	−4.8-3.1
Placebo group			
Median	37.6	36.9	−0.8
Range	31.6-42.2	29.6-41.5	−5.2-2.6

Values are g/L.

*Calculated on basis of individual values.

weeks after the initiation because of an impairment in an enduring depression. This patient received zinc and is included in the investigation. No side effects that could be attributed to the tablets were noticed.

DISCUSSION

Tinnitus is a symptom frequently encountered in diseases of the labyrinth, the eighth cranial nerve, and central communications. No pathophysiologic explanation of the nature of tinnitus is available; this uncertainty is reflected in the many forms of treatment that have been proposed, often with contradictory results.[7] Investigations on animal models indicate that tinnitus is of cochlear origin.[8] One of the theories[9] is based on the assumption that minor traumata in the organ of Corti or pressure on the eighth cranial nerve might cause spontaneous activity in the cochlea. Normally, this activity is not perceived as sound, but it may be spread to other nerve fibers, resulting in tinnitus.

The recommended daily allowance of zinc in adults is 15 mg.[10] The majority of the zinc content in humans is bound to proteins in the tissues. In plasma, zinc is primarily bound to albumin; less than 2% of zinc in the organism is found free in plasma.[10] The zinc level in serum is not a good parameter, but is the most reliable one for assessing the zinc balance in the organism.[2] The metabolism of zinc in the inner ear is described by Prasad.[11]

Some years ago Shambaugh[5] published a report in which a positive effect of zinc in some patients with severe tinnitus was found. Later, Gersdorff et al[3] found a connection between tinnitus and a low level of zinc in serum. They found that 68.7% of 115 patients with tinnitus had hypozincemia. By the administration of zinc tablets in 4 to 10 times the recommended daily allowance for 3 to 6 months, Shambaugh[12] found an improvement in tinnitus in 25% of patients with tinnitus and hypozincemia. Nobody experienced cessation of tinnitus. The investigation of Gersdorff et al[4] with the administration of zinc in 27 patients with tinnitus and hypozincemia showed a good improvement in 4 patients (15%) and a lesser improvement in 10 patients (37%). The trial was not placebo-controlled.

One of the difficulties in assessing a possible effect in the treatment of tinnitus is that tinnitus is a subjective phenomenon that only to some extent may be measured.[13] We therefore chose to assess a possible effect of treatment by the patient's own judgment alone. The investigation from Gersdorff et al[4] was arranged in the same way.

Our investigation could not confirm the high incidence of hypozincemia in patients with tinnitus as reported by other authors.[3,12] Only one patient in our trial presented hypozincemia. That patient received zinc but without any effect on tinnitus. We found an increase in the zinc level in serum in those patients who received the active treatment. However, no effect on tinnitus was found.

In the investigation from Gersdorff et al[4] all the patients presented hypozincemia; this difference might be an essential reason for a result different from ours. However, the report from Gersdorff et al was not a placebo-controlled trial.

From our investigation we may conclude that hypozincemia is not a common finding in patients with tinnitus and that the administration of zinc for 8 weeks has no effect on tinnitus.

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ULTRASTRUCTURE OF CAT SUPERIOR VESTIBULAR COMMISSURAL NEURONS

JEAN-PHILIPPE GUYOT, MD
GENEVA, SWITZERLAND

MICHAEL J. LYON, PHD
SYRACUSE, NEW YORK

RICHARD R. GACEK, MD
SYRACUSE, NEW YORK

The ultrastructure of the feline superior vestibular commissural neurons (CNs) was studied after labeling by contralateral injection of horseradish peroxidase. These small spindle-shaped cells are found in clusters oriented in a rostrocaudal, dorsoventral, or lateromedial direction. The CNs have a cleft nucleus, with the majority of nerve terminals contacting the CN near the emergence of polar dendrites. Polarization of the afferent synaptic profiles suggests a bidirectional nature of inputs to CNs by the vestibular nerve, contralateral CNs, and/or cerebellar systems. One type of labeled cell does not conform to this pattern, instead resembling a vestibulo-ocular neuron. Hence, it may function as a commissural and a vestibulo-ocular neuron. Characterization of different types of synapses, based on the size and eccentricity of their synaptic vesicles, indicates a continuum rather than separate populations. Volume fraction of intracellular organelles showed a larger volume fraction percent of polyribosomes in larger cells. Since this organelle is involved with protein synthesis, this finding may indicate that larger CNs have a more extensive dendritic tree.

KEY WORDS — cat, quantitative ultrastructural data, superior vestibular nucleus, vestibular commissural neurons, volume fraction.

INTRODUCTION

Commissural connections between vestibular nuclei (VN) have been demonstrated by anatomic and physiologic methods. Anatomic demonstrations based on degeneration[1-3] or retrograde transport of horseradish peroxidase (HRP)[4,5] indicate that the majority of commissural neurons (CNs) are located in the superior (ventromedial and ventrolateral areas) vestibular nuclei (SVN) and medial VN, with a smaller number in the descending and group Y nuclei. No commissural projection has been found between the lateral VN.[4,5]

Contralaterally induced electrical activity in the VN has been recorded.[6-8] Weak stimulation of the contralateral vestibular nerve suppresses spontaneous discharge of tonic and kinetic type I neurons while the type II neurons are excited. The activation of type II neurons occurs slightly earlier than the inhibition of tonic type I neurons. Thus, it has been postulated that the commissural pathway for tonic type I neurons is mediated by one or two synapses along its path from the vestibular nerve, an inhibitory neuron being located ipsilaterally to the type I neuron that receives the commissural inhibition. Some evidence suggests that the type II neurons are internuncial neurons.

The role of commissural connections between VN in compensation following unilateral labyrinthectomy has been investigated.[9-11] After hemilabyrinthectomy, spontaneous activity of ipsilateral type I neurons has been shown to decrease or cease and the neurons no longer respond to angular acceleration. By 4 to 6 weeks, ipsilateral type I neurons exhibit some spontaneous firing and respond, but to a lesser degree, to angular acceleration.[12] These compensatory changes seem to be dependent on the integrity of the commissural system, since these changes do not occur after sectioning of the commissural pathway[13] and destruction of commissural fibers after compensation induces reappearance of postural symptoms.[14]

The goal of this study was to determine if subpopulations of CNs exist and to establish an ultrastructural description of CNs within the cat SVN as a basis for comparison to CNs in postneurectomy animals. It should then be possible to determine if there are any anatomic correlates of vestibular compensation in this specific neuron population.

Results indicate that CNs are small and spindle-shaped, have cleft nuclei, and are oriented in a rostrocaudal, dorsoventral, or lateromedial direction. Afferent synaptic profiles (SPs) are concentrated at the poles of the cells near the emergence of processes extending in the same plane as the soma. Some evidence suggests that subpopulations of CNs may exist. Quantitative morphologic techniques indicated a continuum of synaptic vesicle size and shape, thus preventing the separation of synapses according to function (excitatory, inhibitory) on the basis of these variables.

From the Department of Otolaryngology and Communication Sciences, State University of New York Health Science Center at Syracuse (all authors), and the Veterans Administration Medical Center (Gacek), Syracuse, New York. Dr Guyot is now at the Hôpital Cantonal Universitaire, Geneva, Switzerland. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of SUNY Health Science Center at Syracuse.

REPRINTS — Michael J. Lyon, PhD, Dept of Otolaryngology and Communication Sciences, SUNY Health Science Center at Syracuse, 750 E Adams St, 156 Weiskotten Hall, Syracuse, NY 13210.

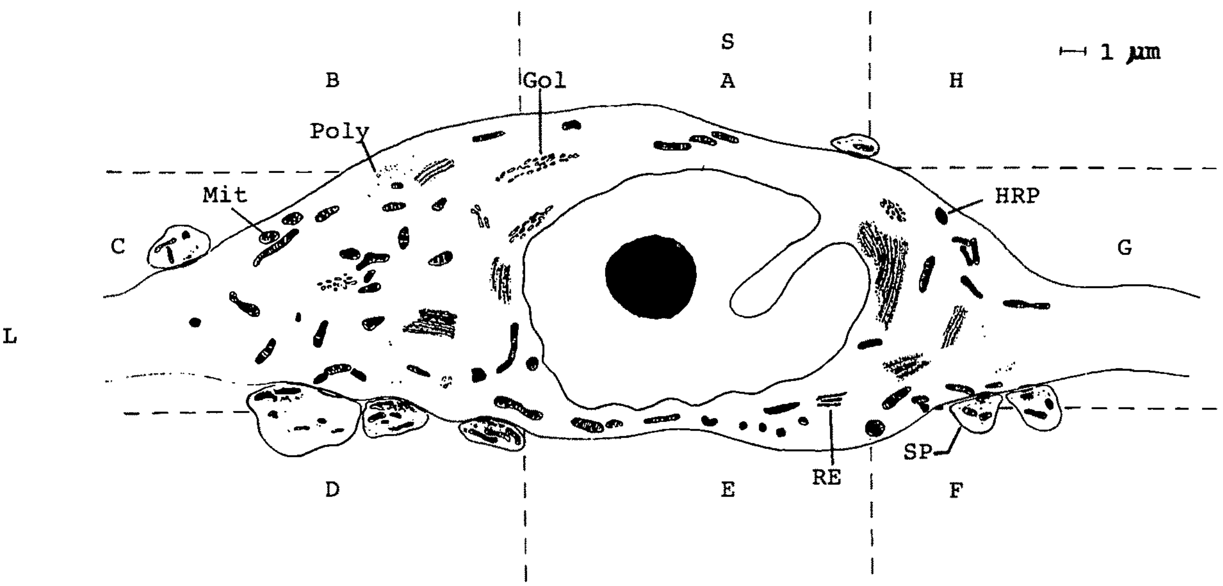

Fig 1. Line drawing depicting general features of superior vestibular commissural neuron and demonstrating how cell soma was divided into eight sections (A-H) for calculation of "local synaptic profile density" by two perpendicular sets of parallel lines running tangential to nucleus. Designated areas B, D, F, and H are considered as transitional areas and are not taken into consideration for this calculation. L — lateral, S — superior, Mit — mitochondria, Poly — polyribosomes, Gol — Golgi apparatus, HRP — horseradish peroxidase, SP — synaptic profiles, RE — rough endoplasmic reticulum.

MATERIALS AND METHODS

Seven adult cats were used in this study. The animals were anesthetized with intravenous Nembutal (30 mg/kg) and intramuscular ketamine (0.75 mL). In the first five animals the brain stem was exposed via a ventral approach. The right submaxillary gland and bone between the auditory bullae were removed. The dura was incised and reflected, and a glass micropipet was inserted into the brain stem approximately 2 mm lateral to the right pyramidal tract, 2 mm caudal to the pons, and to a depth of about 7 mm.[15] The right ventral SVN was hydraulically injected with 2 µL of 20% HRP (Sigma type VI) in 0.9% saline. This surgical approach was chosen to avoid disruption of cerebellovestibular connections. However, this approach was not reliable in that the target was missed in four out of five cats. In two other animals a posterior fossa craniotomy was used. The cerebellum was elevated and a glass micropipet inserted beneath the stria acustica into the ventral SVN. This approach was successful in one of these two cats.

The animals were reanesthetized 18 hours postinjection and perfused with Ringer's solution, followed by 0.12 mol/L phosphate buffer containing 1% paraformaldehyde and 3.5% glutaraldehyde (for details see Gacek et al[16]). Exposure to the double aldehyde solution was limited to 1 hour, at which time the region of the left SVN was removed. The remaining tissue preparation was similar to that used by Gacek et al[16] in the study of vestibulo-ocular (VO) neurons. Briefly, vibratome sections were cut and reacted for HRP activity.[17] Labeled cells were cut out and processed for electron microscopy and ultrathin sections were cut and stained.

Electron micrographs of labeled cells (final magnification, 5,000x) were taken and used to measure cell surface area by means of a Numonics 1224 x-y digitizer. The neuronal volume was estimated by adding surface areas multiplied by the distance between sections, assuming an average section thickness of 60 nm.[18] In order to determine the position of SPs around the soma and to calculate a "local SP density" (LSPD, defined as the number of SPs per 10 µm of membrane) relative to cell orientation (medial, lateral, etc), the cell periphery was divided into eight sections by two sets of perpendicular parallel lines running tangential to the nucleus (Fig 1). Only SPs at the level of the nucleus were used in this calculation. An SP is defined as a structure containing at least five vesicle profiles and displaying typical presynaptic and/or postsynaptic densities.

The periphery of the soma was examined (40,000x) and an electron micrograph taken of each SP in contact with the soma on that grid. Random sections at least 1 µm apart were examined throughout the extent of the neuron. A replica grid (2,160 lines per millimeter) was used to calculate magnification.

Point Counting. Electron micrographs of three sections (one caudal, one rostral, and one through the nucleolus) from each cell were taken and printed and montages were assembled (15,000x). The volume fraction of the nucleus, nucleolus, mitochondria, rough endoplasmic reticulum (RER), smooth endoplasmic reticulum (SER), polyribosomes, lysosomes, Golgi apparatus, multivesicular bodies, and coated vesicles for each cell were calculated by point-counting techniques.[16] These data as well as the square areas of the cell, cytoplasm, and nucleus (including nucleolus) were entered into a data matrix and a statistical analysis was performed.

Synaptic Profile Analysis. Negatives of SPs were projected onto a back screen (280,000x to 290,000x) and the major and minor inner axes of the synaptic vesicles were measured with a Numonics 1224 x-y digitizer interfaced to a DEC PDP 11/73 computer. By means of these measurements, eccentricity (e) and area (a) were calculated by using the formulas

$$e = \frac{\sqrt{A^2 - B^2}}{A}$$

and

$$a = \pi(A \times B)$$

where A is the semimajor axis and B the semiminor axis.[19]

Statistical Analysis. Analysis of variance[20] was used to compare groups. Homogeneity of variance was tested with Levene's test.[21] When it could not be assumed that the variances were equal, an ANOVA was performed with the Welch statistical test.[20,22] Tukey's studentized range method was used for multiple comparisons.[21] Significance was established at a probability value of $p < .05$. Pearson's correlation coefficient[20] was calculated for all variables.

RESULTS

These results are based on two animals: cat 1, which underwent a ventral approach, and cat 2, which received a posterior fossa craniotomy. The SVN was divided into three portions: rostral, intermediate, and caudal. The cells from cat 1 were taken from the caudolateral portion of the SVN, while the cells from cat 2 were removed from the rostral, intermediate, and mediocaudal divisions (Table 1).

Size, Shape, and Orientation. In general, the somas of the CNs were elliptical or spindle-shaped (Figs 1 and 2A), with one exception being a large round cell (Fig 2B). Nuclei of CNs exhibited one or two clefts (Fig 2C), with the exception of the large round cell, of which the nucleus was round and nonclefted. The cells from cat 1 tended to be smaller than those of cat 2, with mean volumes of 3.0×10^3 μm^3 and 8.7×10^3 μm^3, respectively. However, cell volume was similar between animals for cells located in similar portions of the SVN (Table 1). The smallest cells were located in the caudal portion of the SVN (mean, $2.99 \pm 2.3 \times 10^3$ μm^3), while the largest cells were located in the intermediate portion (mean, $12.55 \pm 6.1 \times 10^3$ μm^3), and they were significantly different ($p < .05$). Only one cell was examined from the rostral division. Its volume was 5.54×10^3 μm^3.

Labeled cells tended to be in small clusters of two or three with similar orientation and size. In fact, a somato-somatic contact was observed. Dendrites extended in an orientation similar to that of the soma. There may be a single dendrite, two from the same region, two from the same region with an additional dendrite in the opposite direction, or one on either side of the soma running in opposite directions. Several dendrites were examined for a distance of 30 μm and no branching was found.

TABLE 1. CELL LOCATION, ORIENTATION, AND VOLUME

Cat	*Cell Location Within SVN*	*Cell Orientation*	*Cell Volume ($\times 10^3$ μm^3)*
1	Caudolateral	Rostrocaudal	2.46
		Dorsoventral	1.55
		Dorsoventral	0.67
		Dorsoventral	3.04
	Caudolateral	Dorsoventral	2.65
		Dorsoventral	9.90
		Dorsoventral	3.03
		Dorsoventral	1.57
		Lateromedial	2.71
		Mean	3.07
2	Rostral	Lateromedial	5.54
	Intermediate	*	7.46
		†	21.11
		Lateromedial	8.93
		Rostrocaudal	12.70
	Caudomedial	Rostrocaudal	2.25
		Rostrocaudal	3.03
		Mean	8.72

SVN — superior vestibular nucleus.

*Disc-shaped cell in horizontal plane.

†Spherical cell without specific orientation.

Synaptic Profiles. In total, 733 SPs were examined (217 from cat 1 and 516 from cat 2), from which 12,447 synaptic vesicles (2,387 and 10,060, respectively) were measured. The total number of SPs detected for each cell varied between 4 and 232, with the largest cells having the most SPs. While there is no correlation between the cell orientation and the total number of SPs, the LSPD appears to be related to somal orientation: the highest LSPD was observed at the poles of the soma near dendritic branches (mean density, 1.09 at the poles and 0.47 between poles), while few SPs were found in other areas where there was a thin layer of cytoplasm between the nucleus and the postsynaptic density (Fig 2D). One SP was found between two labeled cells (Fig 2E). The LSPD was similar in most regions around the periphery of the round cell.

The distribution of mean vesicle area for each SP was normal (Fig 3A; range, 300 to 1,350 nm^2; mean, 641 $nm^2 \pm 199$). Since the distribution of vesicle eccentricity within each SP was skewed, the median was used to represent this variable for each SP. The vesicle eccentricity ranged from 0.325 to 0.925 (mean, 0.694 ± 0.110) with small peaks at 0.725 and 0.800 (Fig 3B).

Since the SPs could not clearly separate according to vesicle size and shape, the data were analyzed for three groups of vesicles (flat, large round, and small round vesicles; divisions comparable to those found

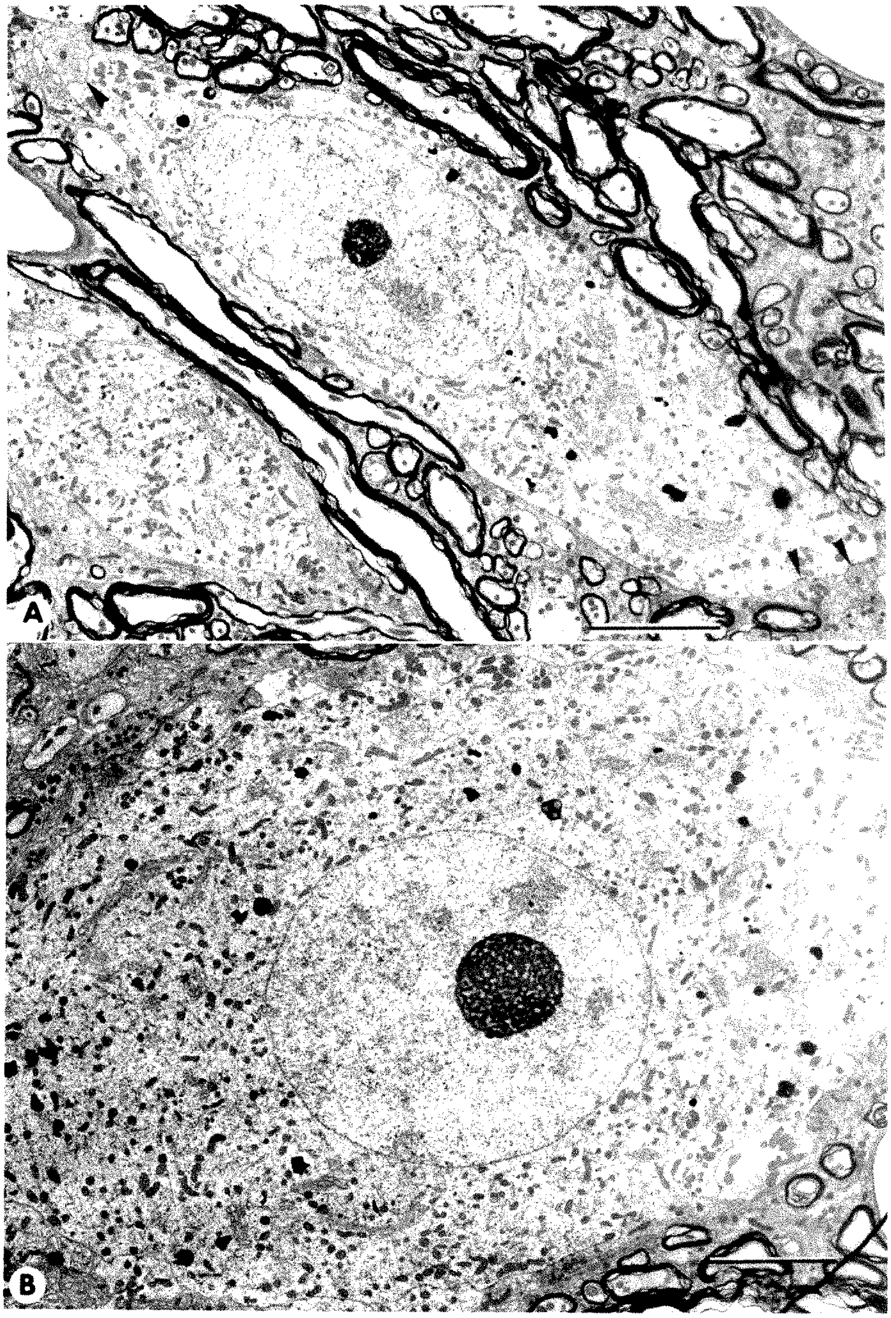

Fig 2. Cell micrographs. A) Typical spindle-shaped superior vestibular commissural neuron (CN) with synaptic profiles mainly at poles (arrowheads). Bar — 5.0 μm. B) This labeled cell does not fit general description of CN. Note round shape and absence of nuclear cleft. It resembles vestibulo-ocular neuron and may function both as vestibulo-ocular neuron and CN. Bar — 5.0 μm. (Continued on next page.)

in the literature[23-25]) by use of cut-points established by K-means cluster analysis.[20] While this technique artificially creates three groups, there is still no clear separation. In addition, when SPs contacting the soma in areas A, C, E, and G (Fig 1) are compared to one another, no significant differences are seen. It appears, therefore, that classification of SPs by vesicle size and shape is not always a valid method.

Point Counting. The results of point counting (Table 2) indicate that the main cellular components are, in decreasing order, the nucleus, nucleolus, polyribosomes, mitochondria, RER, and Golgi apparatus, while lysosomes, multivesicular bodies, SER, and coated vesicles represent minor intracellular components. No significant differences were found for most of the variables when compared between cells or animals with the exception of polyribosomes, which increased as cell size increased. For cells under 400 μm^2 the mean volume fraction percent of polyribosomes was 7.96 ± 2.86. For larger cells, this figure was 14.74 ± 5.53.

DISCUSSION

This study provides a description of the normal ultrastructure of superior vestibular commissural neurons of the cat. Although Korte and Friedrich[24] published an ultrastructural description of the feline SVN, their data included normal and experimental cells (ie, post-unilateral vestibular neurec-

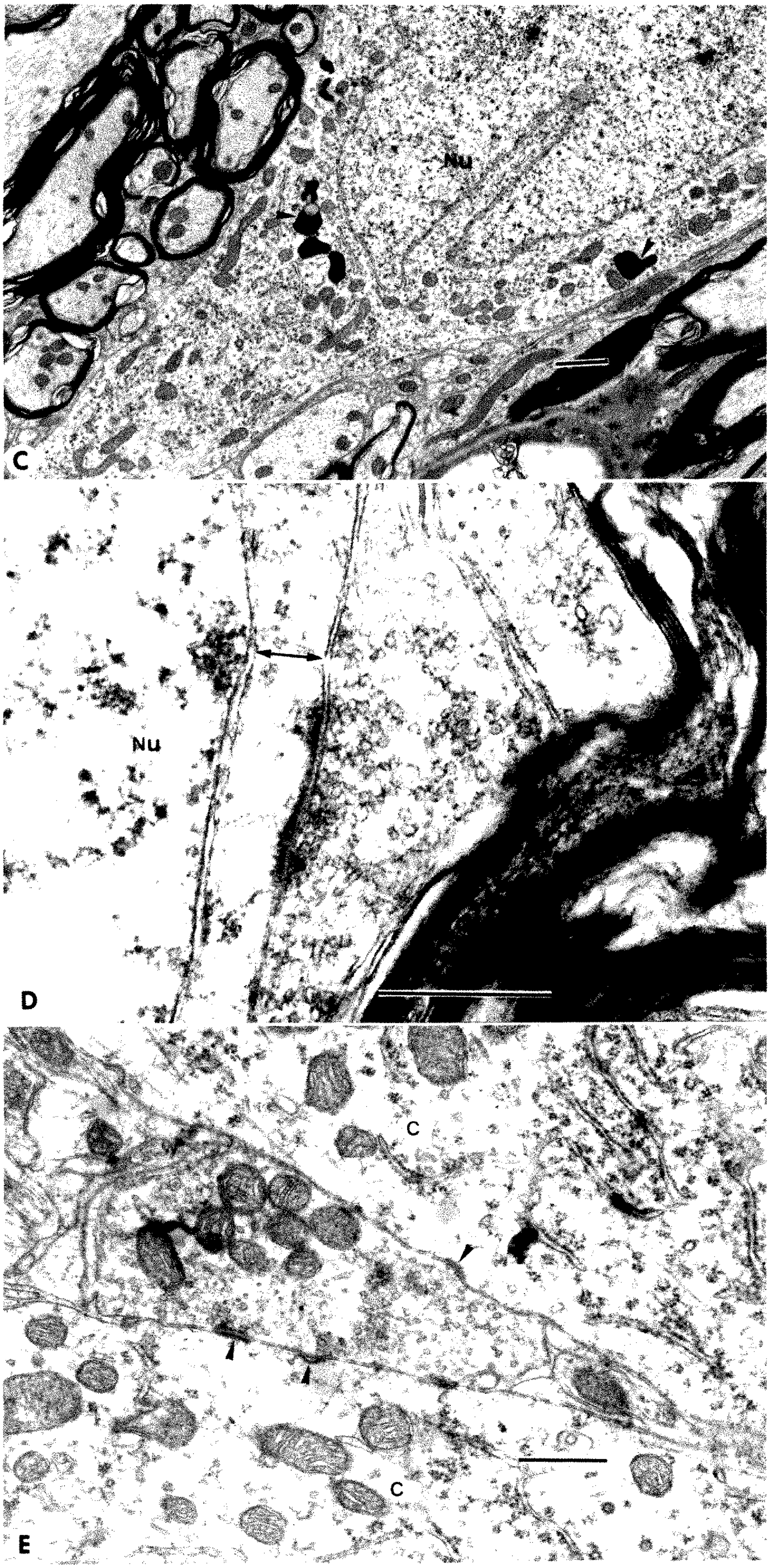

Fig 2 (continued). C) Illustrated in this figure is typical deep cleft in nucleus (Nu). Some horseradish peroxidase-labeled lysosomes are seen (arrowheads). Bar — 1.0 μm. D) Synaptic profile contacting cell soma in C area of Fig 1. Note thin layer of cytoplasm (0.2 μm; arrows) between cell membrane and nucleus (Nu). Bar — 0.5 μm. E) Between two juxtaposed commissural neurons (C), synaptic profile was found having specializations on both somas (arrowheads). Bar — 0.5 μm.

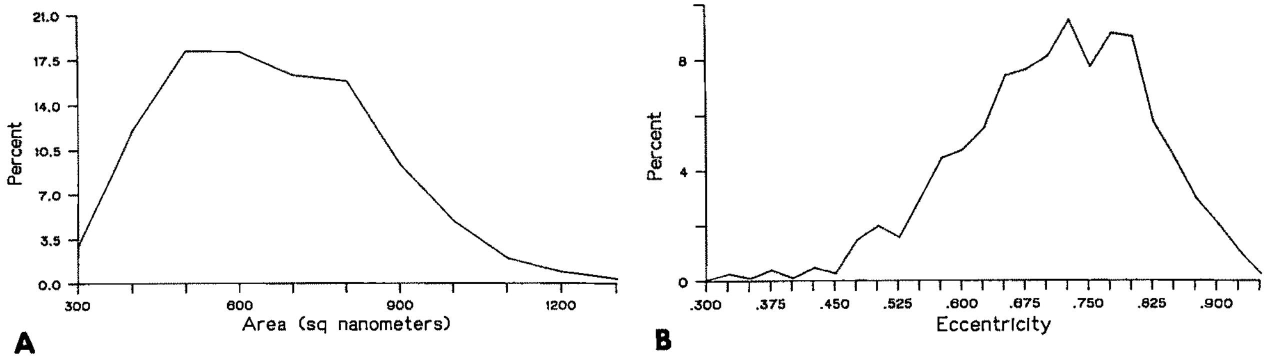

Fig 3. Data for synaptic profiles. A) Plot showing percent distribution of mean synaptic vesicle area for 733 synaptic profiles. B) Distribution curve for eccentricity median of synaptic vesicles contained within 733 synaptic profiles that were examined.

tomy) of unknown type (VO, CN, etc). Morphologic changes, induced by neurectomy, may have occurred in these neurons. In addition, their quantitative analyses are based on only one animal, one side of which was used to evaluate changes after lesion. In the present study, CNs were labeled with HRP, retrogradely transported from the contralateral SVN, to differentiate them from other second-order neurons (VO, vestibulocerebellar, etc) located in the SVN. Previous reports have shown that with the type and extent of injection used in this study that the only neurons labeled within the contralateral SVN will be commissurals.[4]

Only the soma of the CN was studied in detail in order to study a larger number of cells from these animals. A study of SPs on the dendritic trees of these CNs would, because of its time-consuming nature, have limited the study to very few cells.

Organization of Commissural Neurons. The CNs demonstrate several organizational features that may have functional significance. The CNs are located in the peripheral regions of the SVN — primarily lateral and medial areas as described previously.[4] This location is in contrast to that of the VO neurons, which are located in the central and superior regions of the SVN.[16,26] The CNs assume an orientation characteristic of the dendritic poles: dorsoventral, lateromedial, and rostrocaudal axes. This pattern of the dendritic poles provides an arrangement by which the CNs can receive bipolar input,[6,7] that is, input from the ipsilateral vestibular nerve and other input from the commissural fibers. This bipolar arrangement is supported by the polar concentration of SPs at the base of dendritic trees and the paucity of SPs in other locations on the soma. While speculative, this arrangement of soma and SPs suggests that the input from individual vestibular sense organs and perhaps loci within individual sense organs may project over the commissural pathways to second-order neurons (VO) and may possibly allow for inhibition of coplanar canal activity. In addition, the polar concentration of SPs may have further significance in that it has been shown that juxtaposed synapses at the base of dendritic processes may interact in a highly nonlinear way.[27] For example, an inhibitory synapse that increases membrane conductance to an ionic species having an equilibrium potential close to the resting potential of the cell has little effect on the potential but may have a powerful influence in offsetting the depolarization induced by neighboring excitatory synapses.

In agreement with previous descriptions,[28,29] CNs are tightly arranged in groups of two or three. Since the micropipet tract for the injection of HRP into the contralateral SVN exposes a restricted part of the SVN neuropil to the tracer, the grouping of labeled CNs suggests that the projection pattern and termination of the commissural pathway is tightly rather than diffusely organized. The convergence of the system is also supported by the observation of intercalated axonal synapses that would be able to simultaneously and monosynaptically influence two neurons, and by the observation in this study of a somato-somatic contact. Although such contacts have been observed in other systems,[30] they have not been reported until now in the VN of mammals.

It may be expected that cells oriented in the direction of the primary afferents entering the SVN from its lateroventral portion and continuing in a dorsomedial direction[31] would have fewer synapses than those oriented in a transverse plane.[24] Since the total number of SPs does not show any correlation with cell orientation, this study cannot confirm this hypothesis. This lack of correlation may be due to the fact that CNs receive afferents from several sources such as contralateral CNs and the cerebel-

TABLE 2. PERCENT VOLUME FRACTIONS OF CELLULAR ORGANELLES

Variable	*Mean Volume Fraction %*
Nucleus	35.9± 11.5
Nucleolus	0.8± 0.3
Polyribosomes	10.9± 5.1
Mitochondria	10.9± 2.9
Rough endoplasmic reticulum	9.0± 4.2
Golgi apparatus	3.3± 1.0
Lysosomes	1.4± 0.5
Multivesiculated bodies	0.6± 0.4
Smooth endoplasmic reticulum	0.4± 0.4
Coated vesicles	0.3± 0.3

lum.[32]

Physiologic evidence for different functional groups of CNs exists. For example, one type of neuron exerts an excitatory influence on contralateral internuncial neurons — probably type II tonic neurons — which in turn inhibit type I tonic neurons. A second type of neuron produces monosynaptic inhibition on type I kinetic neurons.[6-8]

Morphologic observations from the present study support the suggestion of CN subpopulations in the SVN. First, CNs, like other cells from the intermediate zone of the SVN,[26] are significantly larger than those found in either the caudal or rostal portions. Second, one type of CN that was examined differs considerably from all the others in its volume, total number of SPs, shape, and nucleus and instead resembles a VO neuron.[16] This cell may simply represent the extreme of a range of cells belonging to the commissural category. But the wide disparity in morphology weakens this explanation. This cell may have been labeled via a vestibulocerebellar pathway disrupted during injection. However, this explanation is also unlikely, since it implies a vestibulocerebellar projection that not only reaches the vermis but crosses well beyond the vermis into the VN. Although the CNs are generally smaller than VO neurons, the shape and size of these two populations may overlap, since some VO neurons appear similar to CNs.[16] Therefore, it may be possible that this type of cell projects not only to the contralateral SVN but also to the oculomotor nucleus.

Synaptic Profiles. In an attempt to characterize inhibitory and excitatory synapses on a morphologic basis, the size and shape of synaptic vesicles (generally classified as large round, small round, and flat) have been studied in several species and different nuclei,[23-25] but the criteria used to create the categories were not given in these reports. Korte and Friedrich,[24] studying the feline SVN, which included VO neurons and CNs, subdivide synapses into three types based on synaptic vesicle shape and size: large round, small round, and pleiomorphic. However, as stated previously, these data were established on the basis of one animal, with SPs of a second animal being "visually" classified into these three categories. While their graphs plotting mean vesicle size and shape of individual SPs suggest the presence of two populations based on shape (ie, flat and round), there is a fair amount of overlap in their size data.

Results of the present study do not confirm those of Korte and Friedrich[24] and instead indicate a normal distribution of vesicle area and suggest the possibility of two populations based on eccentricity, but the division between these populations is subtle and a great deal of overlap exists. The fact that we have examined only CNs may possibly explain these differences. It may be that the CNs receive a more diverse set of inputs than the VO neurons and therefore would exhibit more SP diversity. Another explanation could be the different methods used in these studies. While efforts were made in this study to use a method as close as possible to that of Korte and Friedrich,[24] it is possible that the HRP histochemical parameters change the osmotic environment of the vesicles.[33] However, this is unlikely, since the membranes should remain osmotically active until osmication.[34] Other explanations might be taken into account, such as the magnification used for the measurement of the vesicle axes (an apparently round structure observed at a low magnification will exhibit some shape deformity at a higher magnification) and the use of anesthesia for 2 consecutive days in the present study. Therefore, it appears that is is not possible to distinguish different populations of SPs on the basis of vesicle size and shape — a conclusion similar to that of Rastad.[35]

The results of point-counting data did not show any significant difference between cells for most organelles with the exception of polyribosomes. Polyribosomes are concerned with the synthesis of proteins. Since the majority of proteins synthesized by neurons are devoted to the maintenance and renewal of protoplasm,[25] the larger volume fraction of polyribosomes measured in the larger cells may indicate that this cell type has a more extensive dendritic tree than the smaller cell type.[28]

CONCLUSION

Most CNs in the SVN are spindle-shaped and have a cleft nucleus. The CNs in intermediate SVN are larger than those in the rostral or caudal areas. The CNs are oriented in three directions (rostrocaudal, dorsoventral, lateromedial). The majority of afferent synapses are at the cell poles, near dendritic processes that extend in the same direction as the soma. Polarization of the SPs suggests a bidirectional nature to the inputs to the CNs by the vestibular nerve, contralateral CNs, and/or cerebellar systems. Determining the source of these inputs will require demonstration by experimental methods such as ablation of the vestibular nerve or commissural or cerebellar projections. One cell does not conform to the general pattern and resembles a VO neuron. It may be possible that this type of cell projects not only to the contralateral SVN but also to the oculomotor nucleus. This hypothesis could be tested by double labeling techniques. Since analysis indicates a continuum of synaptic vesicle size and shape, classification of the afferent synapses on the basis of their vesicular content could not be accomplished.

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PRESSURE CHAMBER TYMPANOMETRY IN DIVING CANDIDATES

AVI SHUPAK, MD
HAIFA, ISRAEL

ZOHARA SHARONI, BSC
HAIFA, ISRAEL

ERVIN OSTFELD, MD, MSC
HADERA, ISRAEL

ILANA DOWECK, MD
HAIFA, ISRAEL

The currently recommended examination for diving fitness ascertains middle ear autoinflation ability only under surface pressure conditions. The purpose of our study was to document and quantify middle ear pressure equalization failure during simulated dives among diving candidates who had otherwise met the otologic criteria for diving fitness. Forty-two candidates for regular naval diving activity were included in the study. Tympanograms of both ears at 1 and 1.1 absolute atmospheres (ATA) were taken inside a pressure chamber with the subjects in two positions: seated and supine. At a pressure of 1 ATA, type A tympanograms were found in all 84 ears examined. At a pressure of 1.1 ATA, with subjects in the upright position, 19 (22.9%) of the ears had type C and 2 (2.4%) type B tympanograms, while with subjects recumbent during descent, 6 of the ears (7.2%) had type C and 7 (8.4%) type B. Our results suggest that successful autoinflation at surface ambient pressure does not necessarily reflect middle ear pressure equalization ability during descent in a dive.

KEY WORDS — barotrauma, diving, eustachian tube function, middle ear pressure, tympanometry.

INTRODUCTION

The increasing worldwide popularity of self-contained underwater breathing apparatus (scuba) diving has led to a growing awareness of the potential hazards to the diver's well-being and consequently to the establishment of guidelines for the medical examination of sport divers.[1] Barotrauma of the middle ear during descent, caused by failure to equalize the pressure between the middle ear and the ambient environment, is the most common disorder occurring in divers.[2] Accepted criteria for otologic fitness for diving include normal morphologic condition and movement of the tympanic membrane, as evaluated by pneumatic otoscopy; normal function of the eustachian tube, as concluded from outward bulging of the eardrum during the Valsalva maneuver and tympanometry; and normal audiometry.[3] Clinical experience in the management of diving-related otologic injuries has led to the impression that normal otoscopic examination and tympanometry at the surface suggest a lessening of the likelihood of diving middle ear barotrauma but do not preclude its occurrence. This implies that a more sensitive diagnostic tool might be required for the identification of candidates prone to middle ear barotrauma.

The purpose of the present study was to document and quantify middle ear pressure equalization failure, as assessed by tympanometry during simulated dives to 1.1 absolute atmospheres (ATA) in a dry hyperbaric chamber, among diving candidates who had otherwise met the above-mentioned otologic criteria for diving fitness.

STUDY POPULATION AND METHODS

Forty-two candidates for regular naval diving activity, ranging in age from 18 to 20 years, gave their written informed consent and were included in the study. All had previous scuba diving experience and were found fit to dive by a routine pre–diving selection examination battery.[1] Tympanometries of both ears were performed randomly and in sequence for each subject at 1 and 1.1 ATA. These were carried out in a dry multiplace pressure chamber with the GSI 1723 middle ear analyzer (Grason Stadler, Inc, Littleton, Mass), calibrated to both the chamber's 230-V power supply and the examination pressure of 1.1 ATA. The calibration steps were as follows:

1. Adjustment of the tympanometer sound pressure level (SPL) for an indication of 85 dB SPL with use of a sound level meter.
2. Adjustment of the tympanometer's 220- and 660-Hz sensitivities for 75 to 80 mV RMS with use of a digital voltmeter.
3. Calibration of the tympanometer span for Y, G, and B modes at 220 and 660 Hz, using test cavities of 0.5 and 2 mL. (Y is the total middle ear admittance; G [conductance] and B [susceptance] are its components.)

The tympanograms were classified as type A, B, or C according to the criteria described in Table 1. Descent to a pressure of 1.1 ATA was carried out at a rate of 7.5 meters sea water (msw) per minute with the subjects in two randomly sequenced positions: seated upright and supine. The subjects were instructed to equalize their middle ear pressure freely, employing the same maneuvers they used while scuba diving. The tympanometer was recalibrated after each descent. The descent was carried out to 1.1 ATA only, in order to avoid the possible risk of eustachian tube locking, which can occur when a pressure difference of more than 90 mm Hg is built up between the tympanic cavity and the nasopharynx.[4] This pressure difference can be

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From the Department of Otolaryngology, Carmel Lady Davis Hospital (Shupak), and the Israeli Naval Hyperbaric Institute (Shupak, Sharoni, Doweck), Haifa, and the Department of Otolaryngology, Hillel Yaffe Medical Center, Hadera (Ostfeld), Israel.

TABLE 1. TYMPANOGRAM CLASSIFICATION WITH GSI 1723 MIDDLE EAR ANALYZER

Type	*Description*
A	Minimum impedance at −150 mm H2O or greater
C	Minimum impedance more negative than −151 mm H2O
B	No observable change in peak pressure from +200 to −400 mm H2O

reached at a depth of 1.18 msw, which is equal to a pressure of 1.118 ATA, if one fails to equalize middle ear pressure right from the beginning of the descent.

The moderate descent rate of 7.5 msw/min is recommended by the *US Navy Diving Manual* for decompression sickness treatment[5] and, from our experience in treating diving casualties, does not usually cause any subjective pressure equalization difficulties. Otoscopic examination of both ears was carried out at the end of each ascent.

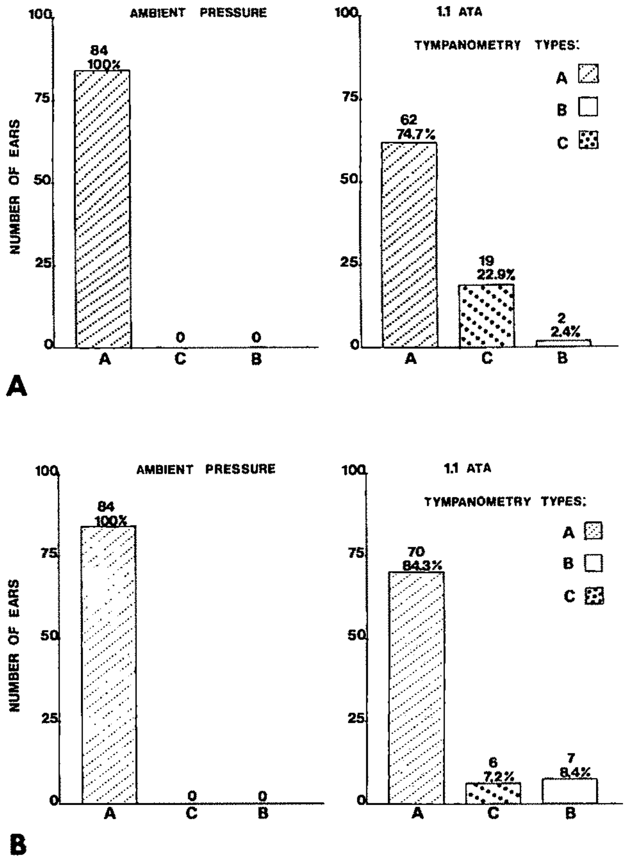
RESULTS

At a pressure of 1 ATA, type A tympanograms were found in all 84 ears examined, with subjects in both the seated and the supine positions. At a pressure of 1.1 ATA with subjects in the upright position, 19 (22.9%) of the ears had type C and 2 (2.4%) had type B tympanograms (see Figure, A) while 6 of the ears (7.2%) had type C and 7 (8.4%) type B when the subjects were recumbent during descent (see Figure, B). One tympanometry measurement at 1.1 ATA was excluded owing to inadequate sealing of the external auditory canal.

With regard to the results at 1.1 ATA, the confidence intervals for the accumulated proportions of type B and C tympanograms were 0.253±0.093 (SD) in the sitting position and 0.156±0.078 (SD) in recumbency. The rate of type B tympanograms was found to be significantly higher in recumbency than in the upright position ($p < .05$, Fisher's exact probability test). The higher rate of type C tympanograms in the upright position did not reach statistical significance (Table 2).

All 19 subjects with initial type C tympanograms finally succeeded in equalizing middle ear underpressure after one to eight repeated attempts, while the 6 individuals with the type B tympanograms were unable to do so.

One of the ears in which a type B tympanogram was found after descent of the subject in the sitting position, and five of the ears in which a type B tympanogram was found after descent of the subjects in recumbency, showed signs of middle ear barotrauma in the otoscopic examinations carried out at the end of the ascent. These included diffuse redness or slight hemorrhage within the tympanic membrane, accompanied by retraction. Treatment by ephedrine hydrochloride nasal drops and a systemic decongestant resulted in complete resolution within 3 to 5 days.



Distribution of tympanometry types at 1 ATA (left) and 1.1 ATA (right). At 1.1 ATA, confidence interval for accumulated proportions of type B and C tympanograms was 0.253±0.093 (A) and 0.156±0.078 (B). A) Upright seated position. B) Supine position.

DISCUSSION

Diving conditions might cause significant difficulties in middle ear pressure-equalization capacity. The relatively marked and rapid pressure changes place an increased physiologic demand on the eustachian tube; hyperbaric chamber tests have shown that higher middle ear pressures are required for active equalization with increasing rates of pressure change.[6] Raising the ambient pressure leads to an increase in tympanic cavity mucosal volume, re-

TABLE 2. CROSS TABULATION OF TYPE B AND C TYMPANOGRAM RATES AT 1.1 ATA IN SUPINE AND UPRIGHT SEATED POSITIONS

	Sitting	
Supine	*Type B Tympanogram*	*Other Tympanograms*
Type B tympanogram	2	5
Other tympanograms	0	76
$p < .05$*		
	Type C Tympanogram	*Other Tympanograms*
Type C tympanogram	2	4
Other tympanograms	17	60
Not significant*		

*Fisher's exact probability test.

sulting in reduced patency of the eustachian tube.[7] Immersion by itself is known to induce elevation of central venous pressure,[8] which is also correlated with an increase in middle ear mucosal volume.[9] Previous studies with various body positions, conducted in dry as well as in wet hyperbaric conditions, have shown that a further increase in central venous pressure caused by the supine and head-down positions frequently assumed in diving leads to significant venous congestion and even greater difficulty in ear clearing.[10-12]

Our observations support earlier studies that showed growing difficulty in middle ear underpressure equalization with raised ambient pressure and supine body position.[11,13] The finding that 2.4% and 8.4% of the ears examined with subjects in the sitting and recumbent positions, respectively, could not reach pressure equalization at 1.1 ATA indicates that the individuals involved are prone to develop ear barotrauma.

During the first stages of a dive, the pressure-volume changes described by Boyle's law are maximal.[14] Under these conditions, the diver does not have many opportunities to clear his or her ears before the raised pressure gradient leads to eustachian tube locking. In this hazardous situation, the eustachian tube cannot be opened by swallowing, while a forceful Valsalva maneuver results in further locking forces and may lead to tympanic membrane rupture or inner ear barotrauma.[4,15,16] This is the reason why 22.9% of the ears examined while the subjects were upright and 7.2% of those examined in recumbency during descent to 1.1 ATA — all of which had type C tympanograms — may also be at risk of developing ear barotrauma in actual diving conditions.

Our results demonstrate that apparent normal eustachian tube function, as defined by an examination carried out at surface ambient pressure in the upright position, does not necessarily reflect adequate middle ear pressure equalization performance during descent. Pressure chamber tympanometry under simulated diving conditions is suggested in order to improve our ability to identify otherwise healthy diving candidates who might be prone to middle ear barotrauma. These candidates may need special attention and follow-up during their training period. Follow-up reports of future middle ear barotrauma events in the study population are required in order to assess whether pressure chamber tympanometry might assist in diver selection.

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CHOANAL ATRESIA AND LYMPHEDEMA

GADY HAR-EL, MD
MARIE L. BORDERON, MD MICHAEL H. WEISS, MD
NEW YORK, NEW YORK

The coexistence of bilateral bony choanal atresia and lower-extremity lymphedema was observed in a family with several consanguineous marriages. The combination of these two rare anomalies, in a hereditary form, has not been described before.

KEY WORDS — CHARGE association, choanal atresia, lymphedema, open bite.

INTRODUCTION

Choanal atresia is a rare congenital malformation with an estimated incidence of 1 in 5,000 to 1 in 8,000 live births.[1-4] The mechanism responsible for the development of choanal atresia is believed to be failure of the breakdown of the bucconasal (buccopharyngeal) membrane by the sixth to eighth week of gestation.[1,3-5]

Choanal atresia is twice as common in females as in males. Most atresias are unilateral (67%) and bony (85% to 90%).[4] Most of the cases are sporadic, but the rare familial occurrence has been reported.[1,6] The coexistence of choanal atresia and other congenital anomalies has been documented in 36% to 45% of patients with unilateral atresia and in 60% to 75% of those with bilateral atresia.[1,3,4] The incidence of associated anomalies is twice as common in males as in females.[4] The list of associated anomalies includes cardiac anomalies, craniofacial anomalies, hypopituitarism, foregut anomalies, cleft lip or palate, hand anomalies, kidney anomalies, facial paralysis, growth and psychomotor retardation, ear anomalies, tracheoesophageal fistula, and various musculoskeletal anomalies.[1-12] Choanal atresia may be included in trisomies 18 and 21 and Turner's and Down syndromes. The term CHARGE association is an acronym for coloboma, heart disease, atresia of the choanae, retarded growth, genital hypoplasia, and ear defects.[1,3-7,10-12] There are no known teratogens accounting for choanal atresia,[1,3] except for a few cases that had been attributed to thalidomide teratogenic effects.[5]

Primary lymphedema is also a very rare disease. The annual incidence is estimated at 1 to 100,000 population under 20 years of age.[13] Fourteen percent of the patients with primary lymphedema have a positive family history.[14] Milroy's (or Nonne-Milroy) disease is a rare disorder characterized by congenital hereditary lymphedema of one or both lower extremities.[14-16] Associated anomalies, such as ocular and eyelid disorders, microcephaly, unusual facial appearance, and genital anomalies, have been reported.[17-20]

FAMILY HISTORY

This is a Yemenite family that immigrated to the United States in 1977. Consanguineous parentage was found in all affected persons (Fig 1). Three members of this family were described in the genetic literature in 1982 as having choanal atresia.[21] Lymphedema, however, was not noticed at that time. No cases of choanal atresia or lymphedema were known in the family before those of generation IV. Cardiologic, audiologic, and nephrologic workup revealed no abnormalities in the affected children except for asymptomatic pericardial effusion in the propositus.

Patient 1 (V 10). The propositus was born in 1976. His parents were first cousins once removed. Pregnancy and delivery were normal. The diagnosis of bilateral bony choanal atresia was made soon after birth and this was corrected surgically at the age of 10 months. At the age of 18 months he was found to have a high-arched palate, hypoplastic nipples, slight pectus excavatum, normal dermatoglyphics, and normal chromosomal study findings.[21] Motor and speech development were slightly delayed. The patient had a second operation for correction of choanal stenosis at age 3. Swelling and edema of both lower extremities developed slowly and the diagnosis of lymphedema was confirmed by lymphangiogram at age 5.

The patient presented to our clinic at the age of 12 years with symptomatic left membranous choanal atresia. At this time we found a well-developed boy with a slight hypertelorism, severe open-bite deformity, high-arched palate, bilateral lower-extremity lymphedema (hard, nonpitting edema), and normal psychomotor development (Figs 2 and 3, left). The atresia was corrected surgically and at the time of this writing, 1 year after operation, the patient remains asymptomatic.

Patient 2 (IV 8). This paternal aunt of the propos-

From the Department of Otolaryngology, SUNY–Health Science Center at Brooklyn and The Long Island College Hospital, Brooklyn (Har-El, Borderon), and the Department of Otolaryngology, Manhattan Eye, Ear and Throat Hospital, New York (Weiss), New York.

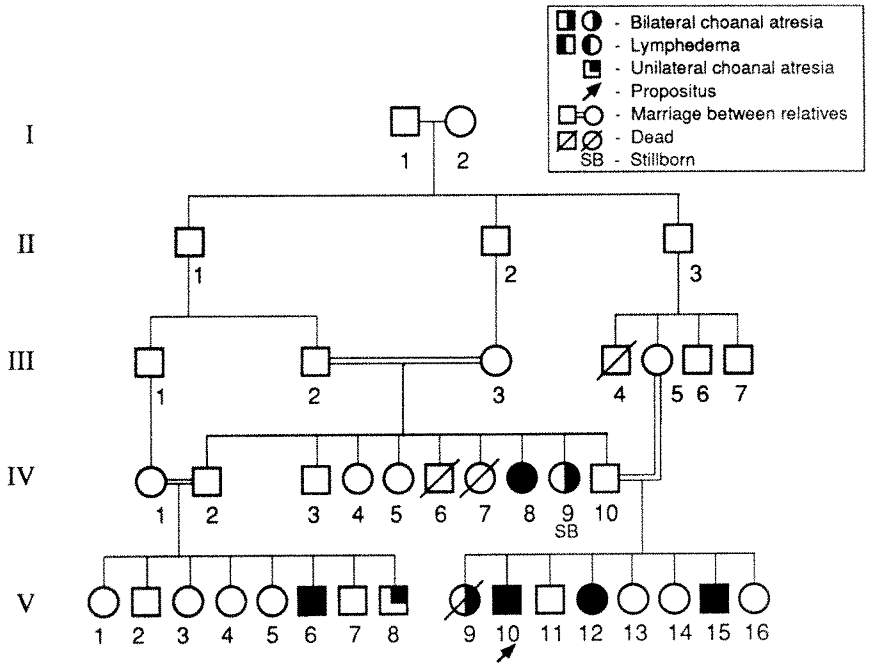

Fig 1. Family pedigree.

itus was born in 1977 after a normal pregnancy. The parents were first cousins. The diagnosis of bilateral, bony choanal atresia was made immediately after birth and corrective surgery was performed at 5 days of age. Bilateral lower-extremity lymphedema was confirmed lymphangiographically at the age of 5 years. Choanal obstruction was removed again at age 10. At present, the patient has no nasal obstruction and has a highly arched palate and hard, nonpitting edema of the lower extremities. Her psychomotor development is normal.

Patient 3 (IV 9). This was a stillborn female with bilateral choanal atresia.

Patient 4 (V 6). This cousin of the propositus was born in 1983. His parents are first cousins. He had three operations for bilateral, bony choanal atresia and recurrent choanal stenosis. At age 6, he presented to our clinic with symptomatic choanal stenosis, highly arched palate, severe open-bite deformity, and hard, nonpitting edema of both feet, but only to the ankle level.

Patient 5 (V 8). This cousin of the propositus was born in 1989 with unilateral, bony choanal atresia and spina bifida. The patient is paraplegic. He has no symptomatic nasal airway problems.

Patient 6 (V 9). This sister of the propositus was born in Yemen in 1975 and underwent surgery for bilateral choanal atresia. She died at 5 months of age. The cause of death is reported as "complications of measles."

Patient 7 (V 12). This sister of the propositus was born in 1979 after an uncomplicated pregnancy and delivery. Bilateral bony choanal atresia was diagnosed soon after birth and a successful operation was performed at the age of 1 month. Her psychomotor development was normal. At 4 years of age, she was found to have lymphedema. This was confirmed by two lymphangiograms at 4 and 5 years of

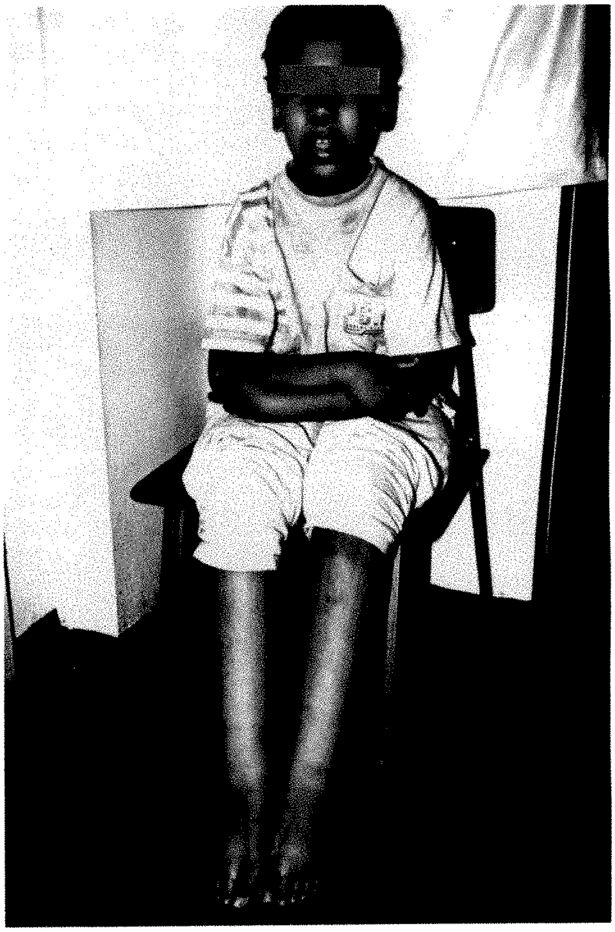

Fig 2. Propositus 3 weeks after surgical correction of membranous choanal atresia. Nasal stents are in place. Note open bite and bilateral lymphedema.

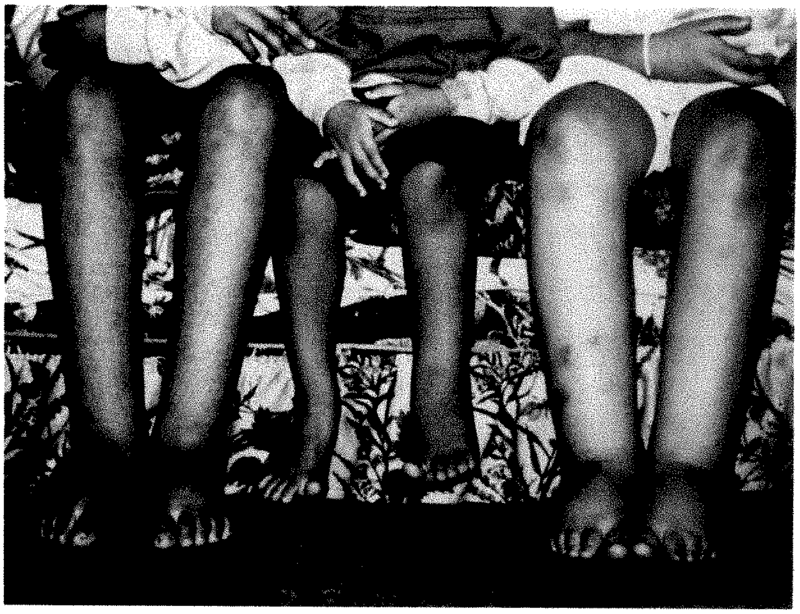

Fig 3. From left to right: propositus, patient V 15, and patient V 12.

age. This patient had two episodes of acute lymphangitis of the lower extremities necessitating admission for intravenous antibiotics. At present, she is a well-developed girl with highly arched palate, no nasal obstruction, and bilateral lower-extremity lymphedema (the most severe in the family) including the thighs (Fig 3, right). She also has diffuse, spotty discoloration of the lower extremities.

Patient 8 (V 15). This brother of the propositus was born in 1985. He underwent surgery for bilateral choanal atresia at the age of 4 months. A second operation for recurrent stenosis was performed at the age of 10 months. His psychomotor development was normal. Our first examination of this patient, at 4 years of age, revealed a well-developed boy with a normal nasal airway and hard, nonpitting edema of the left lower extremity (Fig 3, center).

DISCUSSION

There are several reports in the literature of choanal atresia occurring in close relatives, suggesting that heredity plays an important role.[1-6] Most of these reports suggest autosomal dominant inheritance.[6,8]

Some studies of families with Milroy's disease have attempted to define its genetic pattern. However, no definite conclusion could be made. Milroy's original family showed a pattern that is incompatible with a classic autosomal recessive or sex-linked mode of transmission.[15] Ersek et al[15] described a family with hereditary lymphedema transmitted in a classic sex-linked pattern. It must be emphasized, however, that most cases of primary lymphedema, like most cases of choanal atresia, are sporadic and have no definite genetic pattern.[1,5,14,15,19-21] Therefore, these anomalies may be described as diseases with a multifactorial or polygenic mode of inheritance.[1,21]

Although 50% of the siblings in the propositus' immediate family (V 9 to V 16) are affected, we believe that the entire family shows an autosomal recessive mode of inheritance, for the following reasons. Fifty-percent occurrence in one family of eight siblings is not a sufficient number for genetic conclusions. In fact, 26.9% (7/26) of the persons in generations IV and V (unilateral atresia excluded) are affected. If only those patients who lived long enough to develop lymphedema are considered, 19.2% (5/26) are affected. These numbers are closer to the expected 25% occurrence in autosomal recessive inheritance. Second, all affected persons had parents who were close relatives. Classically, this is how rare recessive diseases become clinically apparent. In fact, there were no cases of choanal atresia or lymphedema prior to generation IV.

Two possible genetic mechanisms may account for the unusual phenotypic combination in this kindred. One theory is based on the possibility that these were two unrelated recessive anomalies originating in two different populations. Coincidentally, these two recessive genes became frequent in one family. This would be a form of "genetic convergence." It was then that consanguineous marriages took place and the anomalies became phenotypic. The second theory is based on the possibility that a common denominator — a common error in embryogenesis — is responsible for both choanal atresia and hypoplasia of the lymphatic system of the lower extremities. The gene responsible for this error was either a result of a mutation, and therefore this is a real "new" disease, or it was an extremely rare gene and only consanguineous marriage could possibly result in homozygotes with choanal atresia and lymphedema.

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IMMUNOHISTOCHEMICAL LOCALIZATION OF SPLEEN-TYPE PROSTAGLANDIN D SYNTHETASE IN RAT NASAL MUCOSA

MASATO MIWA, MD
NAGOYA, JAPAN

SHIGENOBU IWATA, MD
TOYOAKE, JAPAN

KAZUSHI NIWA, MD
TOYOAKE, JAPAN

IKUKO NAGATSU, MD
TOYOAKE, JAPAN

YOSHIHIRO URADE, PHD
OSAKA, JAPAN

Using the specific antibody of spleen-type prostaglandin D synthetase, we investigated the immunohistochemical localization of this enzyme in rat nasal mucosa. The excised tissues were fixed with 4% paraformaldehyde and immunohistochemically stained by the peroxidase-antiperoxidase method. Formalin-resistant connective tissue mast cells were positive for spleen-type prostaglandin D synthetase.

KEY WORDS — nasal mucosa, rat, spleen-type prostaglandin D synthetase.

INTRODUCTION

Prostaglandin (PG) D2 is a cyclooxygenase product formed from arachidonic acid. Although prostaglandins and leukotrienes reveal numerous kinds of physiologic activity, D-series PGs were once thought to be biologically inactive, and of minor importance compared with PGs in the E and F series.[1]

Various kinds of pharmacologic activity of PGD2 have recently been discovered, such as inhibition of platelet aggregation,[2] vasoconstriction and/or vasodilatation,[3] antineoplastic effects,[4] and sleep induction.[5]

Contraction of airway smooth muscle is caused by PGD2 as well as airway vasculature.[6] Prostaglandin D2 thus seems to be an influential mediator in various steps of allergic or inflammatory courses in the airway; however, the physiologic role of PGD2, especially in the upper airway, is still obscure. Prostaglandin D2 is generated after activation of mast cells with anti-immunoglobulin (Ig) E.[7] It is enzymatically formed mainly by two different types of PGD synthetase: PGH-D isomerase (EC5.3.99.2)-glutathione (GSH)-independent PGD synthetase purified from rat brain[8] and GSH-requiring PGD synthetase purified from rat spleen.[9] In this study, we investigated the immunohistochemical localization of spleen-type PGD synthetase in adult rat nasal mucosa in order to verify the physiologic participation of PGD2 in the nose.

MATERIALS AND METHOD

Antisera. Highly specific polyclonal antibodies of rat spleen PGD synthetase were prepared in rabbits. Preparation procedures and characterization of these antibodies have been described previously.[9]

Preparation of Tissue. Five adult female white rats (Wistar strain), weighing 180 to 230 g, were used in this study. Under ether anesthesia, the rats were injected in the heart with a fixative containing 4% paraformaldehyde in 0.1 mol/L phosphate buffer (pH 7.4). After painless decapitation the spleen and anterior portion of the nasal respiratory mucosa were removed.

For the immunohistochemical procedure, tissues were rinsed several times with 0.1 mol/L phosphate buffer (pH 7.4) containing 5%, 10%, and 20% sucrose solution. The frozen tissue sections were prepared with a cryostat for light microscopic immunocytochemistry.

Immunocytochemical Procedure. The floating sections, which were not yet embedded on slides, were immersed for 3 days in 0.01 mol/L phosphate-buffered saline (PBS) containing 0.5% normal goat serum and 0.3% Triton X-100. The sections were then washed with PBS and immersed in freshly prepared 0.3% H_2O_2, which was stirred for 1 hour at room temperature. They were subsequently incubated at 4°C for 4 days with anti-PGD synthetase (spleen-type) serum diluted to 1:1,000 with 0.1 mol/L PBS containing 0.5% normal goat serum, 0.3% Triton X-100, and 0.1% sodium azide. Then followed incubation at room temperature for 1 hour each with goat anti rabbit immunoglobulin (Miles-Yeda) diluted to 1:200 and rabbit peroxidase-antiperoxidase (PAP) complex (DAKO), also diluted to 1:200.

The final peroxidase reaction was induced at room temperature by oxidation for 10 minutes in 0.04% 3.3′-diaminobenzidine tetrahydrochloride (DAB, Sigma) containing 0.01% hydrogen peroxide. The 0.1 mol/L PBS-rinsed floating sections

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From the Department of Otolaryngology, Daido Hospital, Nagoya (Miwa), the Departments of Otolaryngology (Miwa, Iwata, Niwa) and Anatomy (Nagatsu), Fujita Health University, Toyoake, and the Department of Enzymes and Metabolism, Osaka Bioscience Institute, Osaka (Urade), Japan.
REPRINTS — Masato Miwa, MD, Dept of Otolaryngology, Fujita Health University, Toyoake, Aichi, 470-11, Japan.

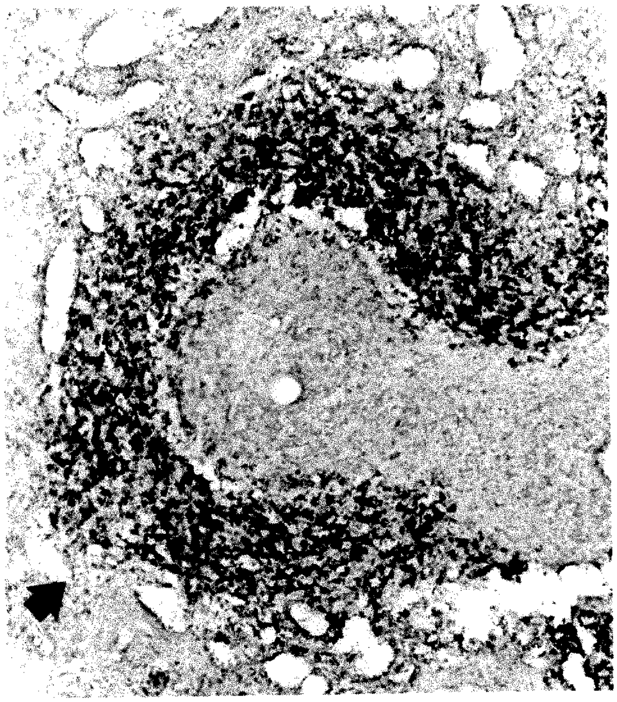

Fig 1. Prostaglandin D synthetase in adult rat spleen (original x200). Peroxidase-antiperoxidase staining showing strongly positive stained cells (arrow) in red pulp of rat spleen.

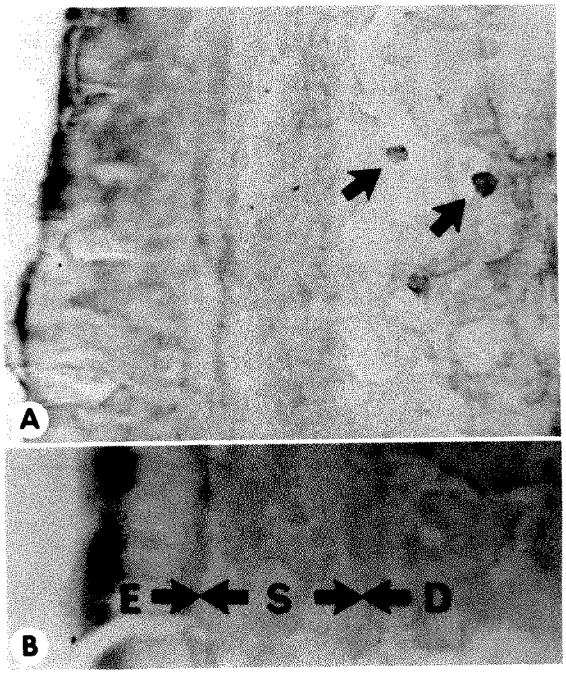

Fig 2. Prostaglandin D synthetase in adult rat nasal mucosa (original x400). A) Peroxidase-antiperoxidase immunohistochemical demonstration of spleen-type prostaglandin D synthetase fixed with 4% paraformaldehyde. Infiltrating cells (arrows) in deep layer of lamina propria are positive for spleen-type prostaglandin D synthetase. No positive cells in epithelial layer or superficial layer of lamina propria. B) Control specimen, treated with anti-rat spleen prostaglandin D synthetase-free serum, shows no specific immunostaining. E — epithelial layer of lamina propria, S — superficial layer, D — deep layer.

were counterstained with hematoxylin, mounted on slides, air dried, and photographed by using a microscope. Toluidine blue staining (pH 2.5) was also done in the same sections of nasal mucosa.

RESULTS

In PAP staining, strongly positive stained cells were observed in the red pulp of rat spleen (Fig 1). In adult rat nasal mucosa, infiltrating cells in the deep layer of the lamina propria were immunohistochemically positive for spleen-type PGD synthetase (Fig 2A). These positive cells were identified as monocytes after counterstaining with hematoxylin. There were no positive cells in the epithelial or superficial layers of the lamina propria (Fig 2A). Metachromasia was found in the infiltrating cells near blood vessels and glands of the lamina propria after staining adult rat nasal mucosa sections with 0.01% toluidine blue (pH 2.5). While the PGD synthetase-positive cells exhibited metachromasia, some metachromatic cells were negative for PGD synthetase in PAP staining. No control specimen, treated with anti-rat spleen PGD synthetase-free serum as the substitute, revealed specific immunostaining (Fig 2B).

DISCUSSION

The tissues rich in GSH-requiring PGD synthetase, such as spleen, thymus, bone marrow, intestine, skin, stomach, and lung, contain an abundance of reticuloendothelial system cells.[10] In this study, we employed for the first time the immunohistochemical staining of spleen as the positive control. There were many PGD synthetase-positive cells, especially in the red pulp — a finding also arrived at and presented in a different paper by one of the authors.[11] Mast cells can be discriminated from basophils by their mononuclear pattern with small fine granules distributed near the plasma membrane.[12] On the basis of this criterion, the PGD synthetase-positive cells we found in nasal mucosa were judged to be mast cells. This finding confirms results of a previous immunohistochemical study of PGD synthetase in rat skin.[13] There are two types of mast cells in rat tissue: mucosal mast cells and connective tissue mast cells (CTMCs).[14] As CTMCs correspond to formalin-resistant mast cells, it is assumed that most of the mast cells in our paraformaldehyde-fixed specimens were CTMCs. Rat CTMCs isolated from the peritoneal cavity are immunologically activated to produce PGD_2.[7]

The results of our study indicate that CTMCs in the upper airway of the rat are immunohistochemically positive for PGD synthetase in PAP staining. Prostaglandin synthetase is found predominantly in the cytosol and not in the microsomal cell fraction, where the enzymes are located that form most of the other PGs.[15] Prostaglandin D_2 might thus have a unique intracellular fraction.[16,17]

After determination of the amounts of primary

PGs formed from endogenous arachidonic acid in homogenates of various adult rat tissues, it was discovered that PGD2 is the major PG in most tissues (50% to 96% of all primary PGs).[10] It was stated that antigen-presenting cells, such as histiocytes and dendritic cells in spleen, thymus, and Peyer's patch of intestine, make up the majority of cells containing GSH-requiring PGD synthetase, and that mast cells are only a minority.[11] But peritoneal mast cells apparently contain spleen-type PGD synthetase and can produce PGD2.[18] We have previously demonstrated cyclooxygenase and PGD synthetase activity in rat and human nasal mucosa using thin-layer chromatography.[19] Although the major source of PGD2 in the nose has not yet been described definitively, we have immunohistochemically verified that mast cells in the rat nasal mucosa contain spleen-type PGD synthetase.

Recent findings show that PGD2 inhalation increases nasal resistance in allergic and nonallergic patients,[20,21] an increase up to 50 times as strong as that induced by histamine.[22]

Tranirast, a drug that inhibits hypersensitivity reactions, suppresses the production of PGD2 in a dose-dependent manner in homogenates of rat peritoneal mast cells.[23] The control of PGD2 production may thus be useful for the treatment of allergic disease affecting the nose. Further studying PGD synthetase will supply significant new findings about the mechanisms of allergy and inflammation in the upper airway.

In conclusion, formalin-resistant mast cells in the rat nasal mucosa have PGD synthetase and may produce PGD2.

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REGULATION OF PHONATORY EFFICIENCY BY VOCAL FOLD TENSION AND GLOTTIC WIDTH IN THE EXCISED CANINE LARYNX

DAVID H. SLAVIT, MD
BROOKLYN, NEW YORK

THOMAS V. MCCAFFREY, MD, PHD
ROCHESTER, MINNESOTA

An excised canine larynx was used to assess the effects of glottic width and vocal fold tension on acoustic power, aerodynamic power, and vocal efficiency. Multiple regression analysis of the data obtained from 10 larynges revealed that with increased vocal fold tension there is a logarithmic decline in radiated acoustic power, while aerodynamic power remains constant ($p < .05$). Vocal efficiency has a similar logarithmic decrease with increased tension ($p < .05$). With narrowing of the glottis, the acoustic power increases more than the aerodynamic power delivered to the larynx, and the efficiency increases. The inverse relationships glottic width has with acoustic power and vocal efficiency are best described by a reciprocal model ($p < .01$). There is a negative linear relationship between glottic width and aerodynamic power. These results suggest that within the larynx the energy conversion is regulated by glottic aperture and longitudinal vocal fold tension. The optimal width for efficiency appears to be the narrowest width that produces phonation within the modal register, whereas increased tension decreases the efficiency of the glottis.

KEY WORDS — larynx, phonatory efficiency, vocal fold, voice.

INTRODUCTION

The larynx functions as a transducer, converting aerodynamic power provided by the air expelled from the lungs into acoustic power during phonation. Within the larynx, the vocal power produced can be regulated by varying the amount of aerodynamic power that is converted into acoustic power. This ratio of acoustic power emitted from the larynx to aerodynamic power delivered to the larynx is the vocal efficiency of the larynx. Likely control variables for this energy conversion process are the glottic width and vocal fold tension. Vocal intensity can also be regulated by adjusting the aerodynamic power delivered to the larynx by the lungs. By adjusting vocal tract formants to specific harmonics of the source and shaping the glottic flow pulse by source-tract interaction, the supraglottic system can regulate the radiated acoustic power.

This investigation was designed to establish the relationships glottic width and vocal fold tension have with radiated acoustic power and vocal efficiency. Also, the question of whether an optimum glottic width and vocal fold tension exists with respect to phonatory efficiency was examined.

Excised larynges were used for this study. Acoustic power was radiated from the glottis into free space and measured by a sound level meter. The effects of variation of vocal fold tension, glottic width, and airflow rate on vocal efficiency, aerodynamic power, and acoustic power were investigated.

The use of excised larynges provides a setting to test new concepts, while enabling one to manipulate variables not easily controlled in in vivo studies. The dog has been the principal animal model for laryngeal studies.[1-4] Although there are differences between the canine and human larynges in terms of thickness of the vocal folds, histology of the vocal folds, size of the ventricles, absence of a vocal ligament, and position of the cricoid and thyroid cartilages,[5] much information concerning vocal fold physiology has been achieved from the excised canine laryngeal model. As with all models, there are appropriate techniques for such experimentation and limitations to the areas within which the analogy applies.

MATERIALS AND METHODS

Subjects. The larynges were obtained from 10 healthy adult mongrel dogs immediately after they were painlessly killed for organ procurement. These dogs had not undergone any previous experimental studies and had normal larynges on direct examination. The trachea was transected approximately 14 cm below the level of the cricoid cartilage. Superiorly, the incision was between the thyroid cartilage and the hyoid bone, with the soft parts cranial to the level of the ventricular folds removed.

Preparation and Experimental Design. Figure 1 illustrates the experimental setup. The excised larynx model used has been previously described in detail.[6] A cuffed tracheotomy tube was positioned in the trachea with the cuff inflated to form a seal, the tip lying 10 cm below the vocal cords and pointed rostrally. Air supplied from a compressed air canister was heated to 37°C and humidified to >95% relative humidity by being bubbled through a Bennett Cascade unit before being passed up the trachea

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From the Department of Otorhinolaryngology, Mayo Clinic, Rochester, Minnesota. Dr Slavit is currently at the Department of Otolaryngology, Long Island College Hospital, Brooklyn, New York. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the Mayo Clinic.

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REPRINTS — Thomas V. McCaffrey, MD, PhD, Dept of Otorhinolaryngology, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

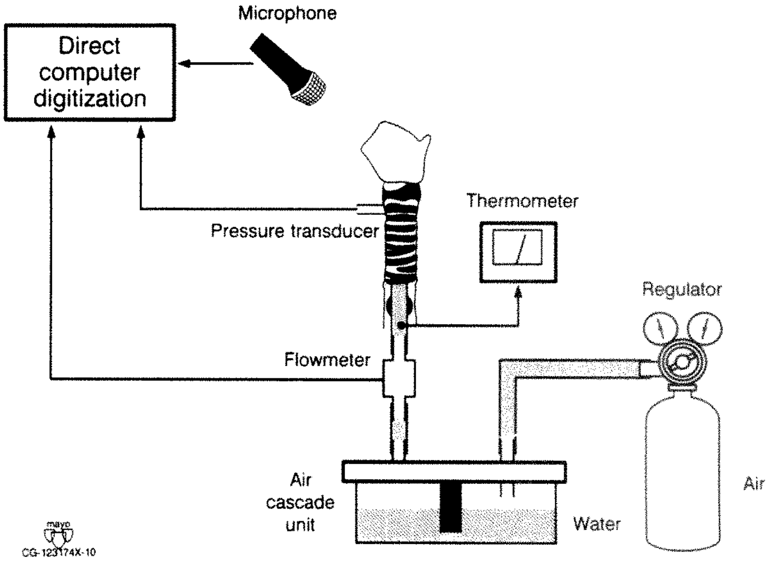


Fig 1. Schematic representation of experimental setup for excised laryngeal preparation.

and through the larynx. Airflow rate was controlled with a valve and measured by a pneumotachograph. The airflow meter was calibrated before every experiment with a Lab-Crest flowmeter. A catheter tip pressure transducer to measure subglottic pressure was placed into the trachea between the cricoid cartilage and the first tracheal ring with its tip 2 cm below the vocal folds. Calibration of the Celestone pressure transducer to 60 and 120 mm H_2O was performed prior to every experiment by means of a pressure gauge. A temperature probe was positioned at the caudal end of the trachea to confirm that the temperature of the air was maintained at 37°C.

Electroglottography (EGG)[7] and photoglottography (PGG)[8] were used to confirm that the vocal folds were vibrating in a pattern consistent with the modal register as opposed to falsetto or vocal fry.[6] Recording electrodes for the EGG (Synchrovoice) were sutured on each side of the thyroid cartilage, symmetrically placed. The ground electrode was secured to adjacent strap muscles. A DC light source was placed above the larynx and a Centronics OSD-2 phototransducer was fixed against the trachea just below the cricoid cartilage to record the PGG signal. The microphone for the Larson-Davis 800B sound intensity meter was mounted a radial distance of 30 cm above the glottis and off-axis to prevent direct exposure to convective airflow. To provide a flat frequency response in the phonation spectrum with suppression of some low-frequency background noise (below 30 Hz), the C scale of the sound intensity meter was used.

The effects of muscular contractions of the cricothyroid muscles, lateral cricoarytenoid muscles, and interarytenoid muscle were simulated by means of surgical silk suture (Fig 2). To simulate the effect of the cricothyroid muscle, a small rectangular segment of thyroid cartilage overlying the anterior commissure was isolated by making horizontal and vertical cuts through the cartilage. A surgical silk was then sutured at one end to the anterior commissure and the incised section of thyroid cartilage, and at the other end the silk was attached to a force transducer (Grass FT03D). The length and longitudinal tension of the vocal folds were altered by applying tension to the suture in the plane of the vocal folds. The adducting force of the lateral cricoarytenoid muscles was simulated by attaching a surgical silk to the muscular process of the arytenoid cartilage and applying force in the medioventrocaudal direction.[6] A surgical silk placed through the posterior aspect of the body of the arytenoids simulated the adduction action of the interarytenoid muscle. To help form the body of the vocal fold, a technique similar to a type I thyroplasty[9] was used with a piece of Silastic placed through a window in the thyroid cartilage. This displaced the muscle and added bulk, and thus helped form the body of the vocal fold.

The experiments were conducted immediately af-

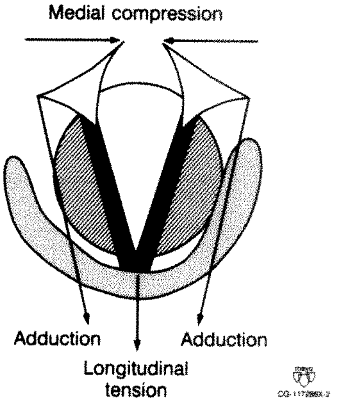
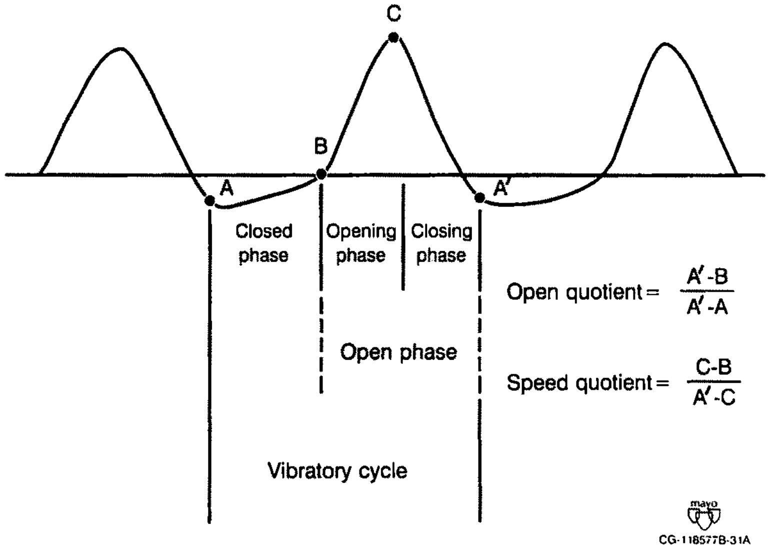


Fig 2. Longitudinal anterior-posterior force on vocal folds simulates effect of cricothyroid muscle. Adduction by lateral cricoarytenoid muscle is simulated by medioventrocaudal force on muscular process of arytenoids. Medial compression of posterior aspect of arytenoids simulates interarytenoid muscle.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Speed quotient = $\frac{C-B}{A'-C}$
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Fig 3. Photoglottographic waveform and glottographic quotients. Period of vibratory cycle can be divided into open and closed portions. Open portion can be further subdivided into opening and closing portions. Open quotient is ratio of open phase to period of vibratory cycle, and speed quotient is ratio of opening phase to closing phase. A, A′ — points of initial glottic closure as lower margins of vocal folds come together, B — point of initial glottic opening as upper margins separate, C — point of maximum glottic aperture.

ter obtaining the larynx, and were completed within 3 hours. Vocal fold tension, glottic width, and airflow rate were systematically varied while the glottographic signals, subglottic pressure, and sound intensity were simultaneously recorded. Vocal fold vibrations were recorded over a broad range of frequencies. To determine if there were changes in the vibratory nature of the vocal folds over the time of the experiment, certain specific configurations of the larynx were retested every 45 minutes and evaluated with respect to frequency, open quotient (OQ), speed quotient (SQ), jitter,

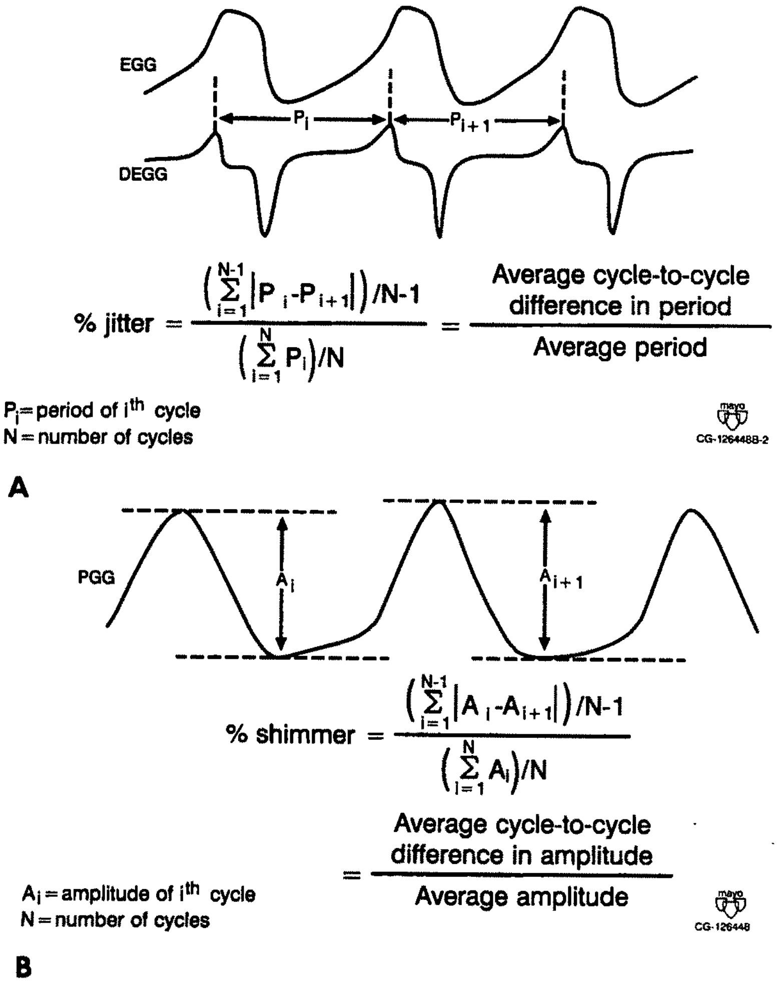
EGG
DEGG
P_i
P_{i+1}
% jitter = $\frac{\left(\sum_{i=1}^{N-1}|P_i-P_{i+1}|\right)/N-1}{\left(\sum_{i=1}^{N}P_i\right)/N}$ = $\frac{\text{Average cycle-to-cycle difference in period}}{\text{Average period}}$
P_i = period of i^{th} cycle
N = number of cycles
CG-126448B-2
A
PGG
A_i
A_{i+1}
% shimmer = $\frac{\left(\sum_{i=1}^{N-1}|A_i-A_{i+1}|\right)/N-1}{\left(\sum_{i=1}^{N}A_i\right)/N}$ = $\frac{\text{Average cycle-to-cycle difference in amplitude}}{\text{Average amplitude}}$
A_i = amplitude of i^{th} cycle
N = number of cycles
CG-126448
B

Fig 4. Computational formulas. A) For jitter. Jitter was determined from electroglottographic (EGG) signal by using first derivative of EGG signal (DEGG) to calculate period of waveforms. B) For shimmer. By using photoglottographic (PGG) signal, amplitude of vocal fold vibration was determined.

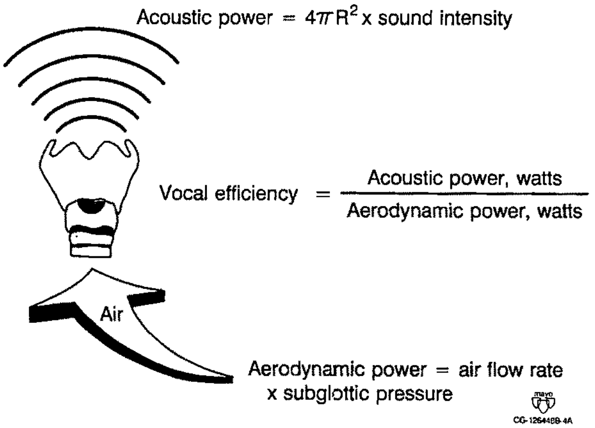
Acoustic power = 4πR² x sound intensity
Vocal efficiency = Acoustic power, watts / Aerodynamic power, watts
Air
Aerodynamic power = air flow rate x subglottic pressure
mayo
CG-1264488-4A

Fig 5. Vocal efficiency is ratio of acoustic power radiating from larynx to aerodynamic power delivered to larynx.

and shimmer (Figs 3 and 4).

Data Acquisition. Photoglottographic[7] and EGG[8] signals were amplified to the ±5-V range and band-pass-filtered with five-pole Butterworth filters at 1.0 Hz and 2.5 kHz. The EGG and PGG signals were then digitized at 10,000 Hz. An AST 20868 microcomputer with an 80287 math coprocessor and ASYSTANT software for high-speed data acquisition and analysis were used. One second of waveform data was stored onto the hard disk of the microcomputer for later analysis. Within each trial of simulated phonation, 20 consecutive waveforms were analyzed and averaged to calculate a single value for OQ, SQ, fundamental frequency (F_0), jitter, and shimmer (Figs 3 and 4). Points of glottic opening and closing were determined as previously described by Berke et al.[2] The signals were also monitored on a Tektronix oscilloscope (model 5111) to confirm modal register.[6,10]

Vocal fold longitudinal tension, airflow rate, subglottic pressure, and sound intensity were recorded simultaneously on a Beckman R611 recorder. The vocal fold length from the anterior commissure to the vocal process and the glottic width at the vocal process were measured with the aid of magnification and recorded manually.

Analysis of Data. First we confirmed Titze's[11] finding that sound radiated from the excised larynx was nearly isotropic, like a pulsating sphere. On the basis of this finding, the sound power radiated from the larynx was calculated from the formula $P_r = 4\pi R^2 I$ where R is the radius in meters (0.3 m), I is the sound intensity in watts per square meter, and P_r is the radiated sound power in watts (Fig 5).

The mean aerodynamic power was calculated by taking the product of subglottic pressure (newtons per square meter) and the airflow rate (cubic meters per second; Fig 5). The aerodynamic power (p_a) was thus expressed in watts.

The vocal efficiency (e) was defined in the usual way as radiated acoustic power divided by aerodynamic power supplied to the larynx ($e = p_r/p_a$).[12]

Multiple regression analysis was performed to determine any statistically significant ($p < .05$) changes in the aerodynamic power, acoustic power, and vocal efficiency with alteration of the independently controlled variables (airflow rate, vocal fold tension, and glottic width). Both linear and nonlinear regression analyses were performed with statistical software.

RESULTS

Ten excised larynges were studied under 50 different combinations of airflow rate, vocal fold tension, and glottic width. The mean frequency of vibration of the vocal folds was 180 Hz. The frequency of vibration for each larynx was varied over a range of 155 Hz.

On the basis of the consistency of the vibratory pattern as measured by F_0, jitter, shimmer, and the glottographic quotients OQ and SQ for the specific test configurations retested every 45 minutes, the vibratory natures of the vocal folds appeared to be constant throughout the experiment (see Table).

Effect of Vocal Fold Tension. As vocal fold tension increased, the frequency of vibration of the vocal folds increased. Alterations in vocal fold tension appeared to have no effect on aerodynamic power (Fig 6A). There was no significant change in either of the components of aerodynamic power (subglottic pressure and airflow rate) with increases in vocal fold tension.

Vocal fold tension had a nonlinear relationship ($p < .01$) with radiated acoustic power (Fig 6B). As tension increased there was eventually a logarithmic decrease in acoustic power. There was an associated decrease in amplitude of vibration of the vocal folds as longitudinal tension was increased, based on the PGG waveform and stroboscopy. This decreased amplitude of vibration accounted for a decrease in acoustic power. The maximal tension value within the modal register was thus not the optimal value for acoustic power radiated from the larynx. A linear model did not fit the data of tension versus acoustic power. This relationship was better de-

ASSESSMENT OF VIBRATORY NATURE OF VOCAL FOLDS OVER LENGTH OF EXPERIMENT FOR FIXED PARAMETERS

Time (min)	*Fundamental Frequency (Hz)*	*Open Quotient*	*Speed Quotient*	*Jitter*	*Shimmer*
0	205	0.66	0.96	1.38%	1.91%
45	202	0.67	0.94	1.80%	1.84%
90	200	0.63	0.94	2.36%	1.67%
135	197	0.63	0.98	1.97%	1.96%
190	198	0.62	0.93	2.39%	2.02%

Airflow 1,000 mL/s, vocal fold tension 1.0 unit (27,759 dynes), glottic width 0.8 mm.

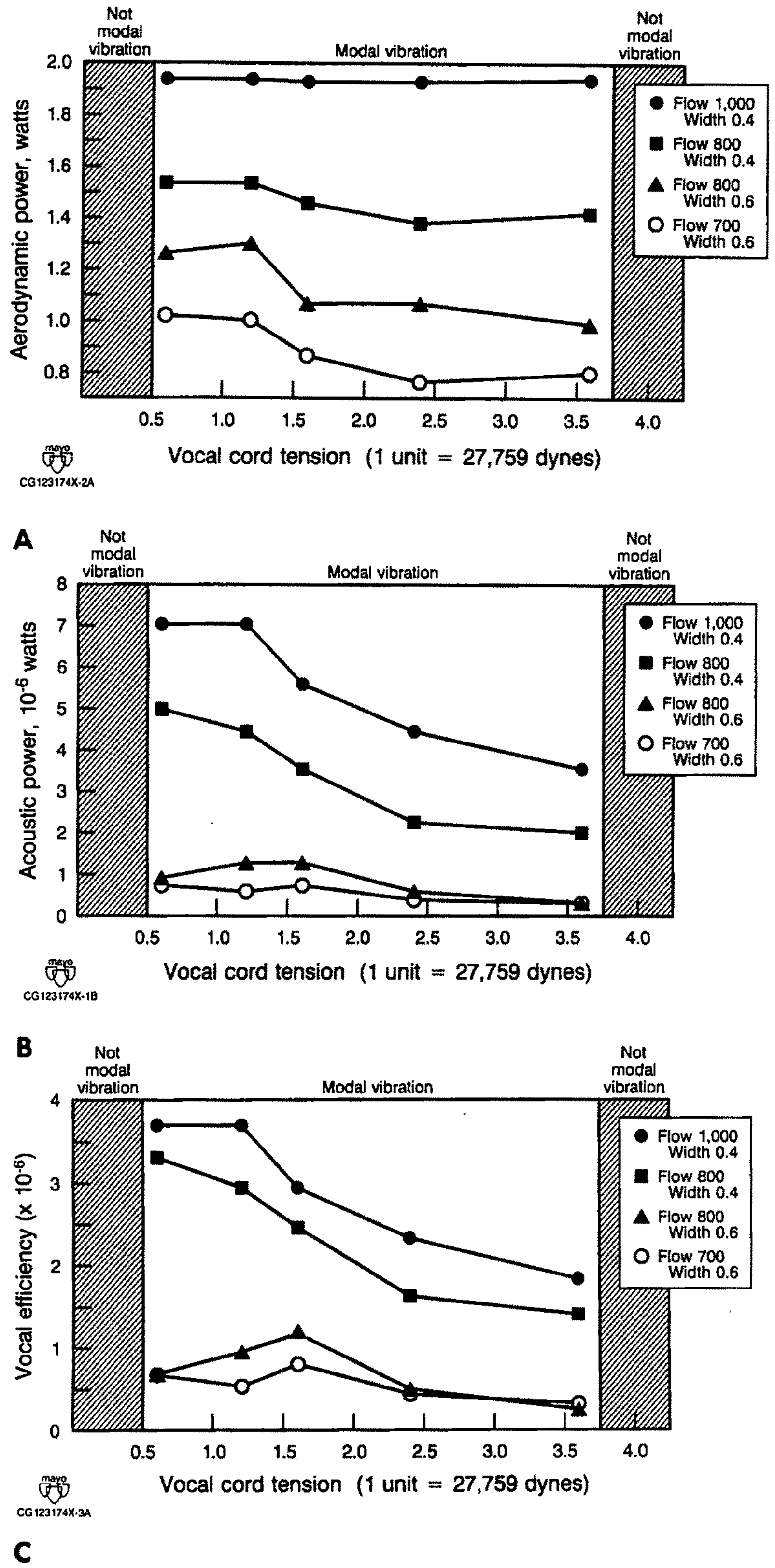

Fig 6. Effect of vocal fold tension for four configurations of glottic width and airflow rate. Note that for tensions below 0.5 unit and tensions above 4 units, vibratory pattern of vocal folds was no longer consistent with modal register (1 unit of tension = 27,759 dynes; flow in milliliters per second; glottic width in millimeters). A) Graph of vocal fold tension versus aerodynamic power. Aerodynamic power remained relatively constant as vocal fold tension changed. B) Acoustic power in relation to vocal fold tension. Note that acoustic power decreased as tension increased. This nonlinear relationship (logarithmic) was statistically significant ($p < .001$). C) Vocal efficiency as function of vocal fold tension. Again note statistically significant ($p < .001$) logarithmic relationship tension had with efficiency. As vocal fold tension increased, vocal efficiency eventually decreased.

scribed by a logarithmic curve, with the acoustic power its lowest value at peak vocal fold tension.

The vocal efficiency had a similar nonlinear relationship ($p < .01$) with vocal fold tension (Fig 6C). This relationship was due to the fact that aerodynamic power remained relatively constant while acoustic power decreased with elevation of tension on the vocal folds. The decrease in vocal efficiency with increased tension in the high end of the modal

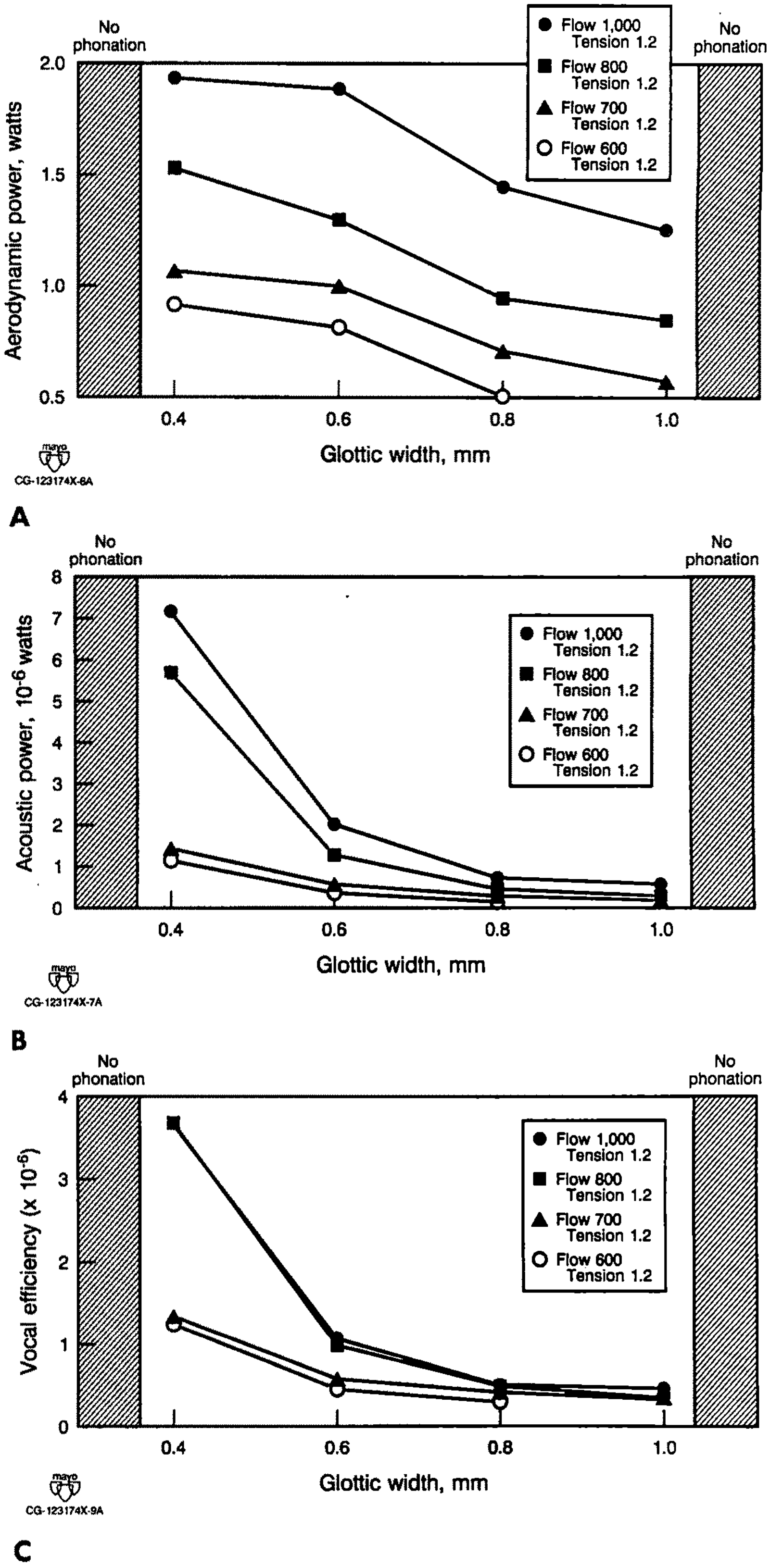

Fig 7. Effect of glottic width for four configurations of vocal fold tension and airflow rate. Note that for extreme abduction and adduction there was no vocal fold vibration or phonation (1 unit tension = 27,759 dynes; airflow in milliliters per second; glottic width in millimeters). A) Glottic width versus aerodynamic power. Width had negative relationship ($p < .001$) with aerodynamic power that best fits linear relationship. B) Figure shows reciprocal relationship between glottic width and acoustic power ($p < .001$). C) Glottic width and vocal efficiency were negatively related. Reciprocal model best fits this relationship ($p < .001$). Narrower glottic width corresponds to greater vocal efficiency.

register was related to the decreased amplitude of vocal fold vibration. Less of the airstream was modulated with the reduced amplitude and thus less acoustic power was produced.

Effect of Glottic Width. Extreme abduction of the vocal folds resulted in a large glottic width with nearly steady airflow and no vocal fold vibrations or phonation. On the other hand, extreme adduc-

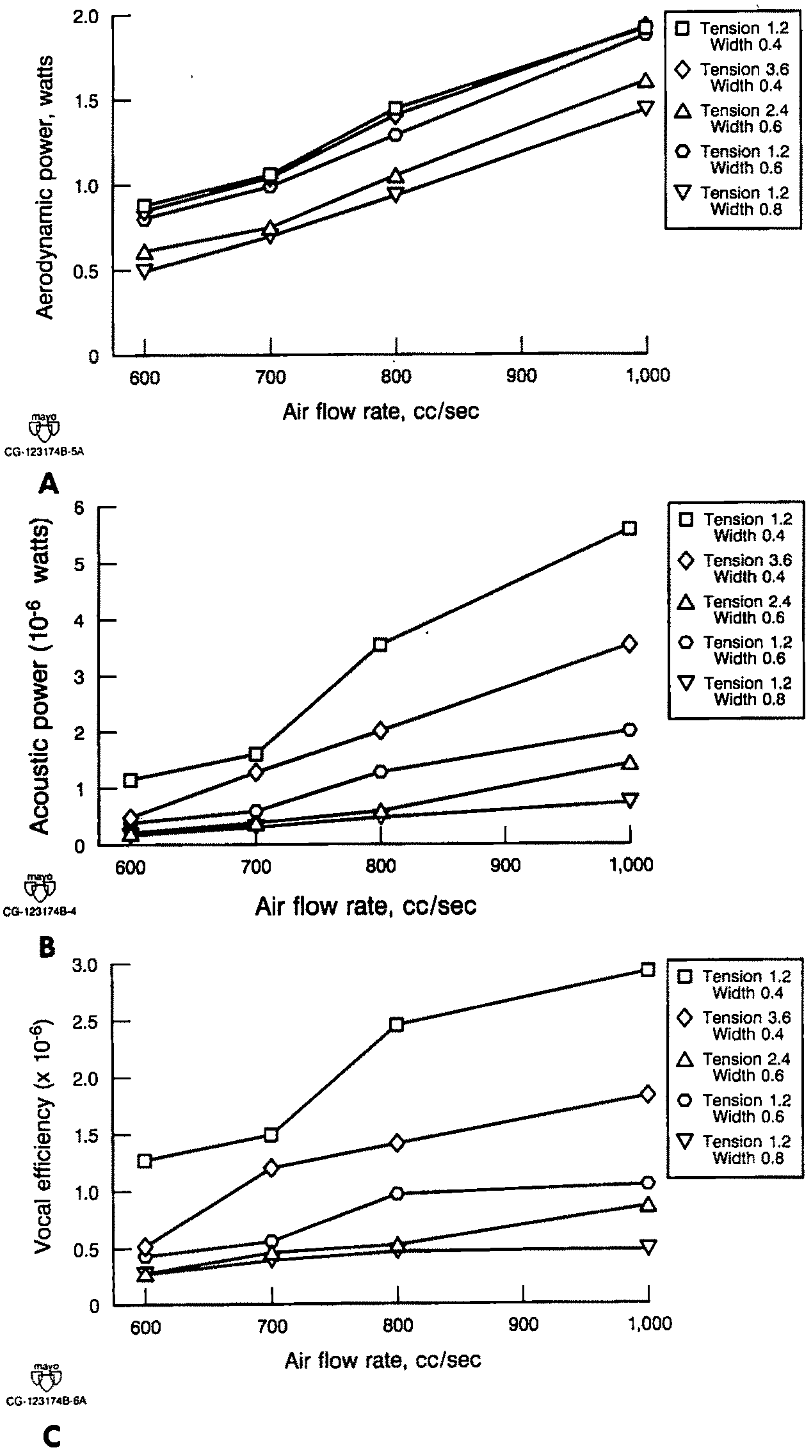

Fig 8. Effect of airflow rate for five configurations of vocal fold tension and glottic width (1 unit tension = 27,759 dynes; airflow in milliliters per second; glottic width in millimeters). A) Airflow rate versus aerodynamic power. Linear direct relationship ($p < .001$) was observed. B) Graph of airflow rate versus acoustic power demonstrates direct nonlinear relationship ($p < .001$). C) Figure shows nonlinear direct relationship ($p < .001$) between airflow rate and vocal efficiency.

tion resulted in complete closure of the glottis with inhibition of vocal fold vibration. Furthermore, with extreme adduction, the deleterious effects of tissue collision and damage due to pressing of the vocal processes are an important consideration. Between these two extremes existed a set of glottic widths for which the vocal folds vibrated in the modal register.[6] Within this region of glottic widths, for a constant airflow the aerodynamic power, acoustic power, and vocal efficiency all increased as the width narrowed. The frequency of vibration also increased as the glottic width narrowed.

Multiple regression analysis of the data demonstrated aerodynamic power to have a statistically significant negative linear relationship with glottic width at constant airflow rates ($p < .001$). Figure 7A shows the increase in aerodynamic power for a decrease in glottic width. Looking at the components of aerodynamic power, a decrease in glottic width caused an increase in subglottic pressure ($p < .001$) but no change in airflow rate, which was held constant. Thus, the negative relationship between glottic width and aerodynamic power was related to the changes in subglottic pressure caused by alteration in glottic width.

The radiated acoustic power also increased as the glottic width decreased (Fig 7B). This relationship was best described by a reciprocal model. This statistically significant relationship ($p < .001$) was a reflection, in part, of the increased subglottic pressure with decreased glottic width, similar to that seen in the relationship between glottic width and aerodynamic power.

Analysis of the vocal efficiency reveals a significant reciprocal relationship ($p < .001$) with glottic width (Fig 7C). Although both the aerodynamic and acoustic power increased with narrowing of the glottis, there was a greater increase in the radiated acoustic power leading to an increase in efficiency. This implied a more efficient energy conversion at narrower glottic widths. Similarly, for an increase in glottic width, the efficiency decreased, reflecting a greater loss in acoustic power than aerodynamic power.

Effect of Airflow Rate. Figure 8A shows the direct relationship ($p < .001$) airflow rate had with aerodynamic power for constant glottic width and vocal fold tension. The nonlinear direct relationship ($p < .001$) between airflow rate and acoustic power is shown in Fig 8B. The increase in both aerodynamic and acoustic power with an increase in airflow rate was related to the increase in subglottic pressure. With respect to laryngeal efficiency, increases in flow rate caused a slight increase in efficiency (Fig 8C). This nonlinear relationship ($p < .001$) demonstrated a greater increase in acoustic power than aerodynamic power for increases in glottic airflow.

DISCUSSION

This work assessed the effect of vocal fold tension, glottic width, and airflow rate on vocal efficiency within the canine modal register. Since the vocal tract was eliminated, there was no control of vocal power by resonance in a supraglottic system. Furthermore, by controlling the airflow rate and the effects of the lungs, the ability of the larynx to regulate vocal power could be isolated. Although in humans the regulation of constant subglottic pressure is probably more important than the regulation of constant airflow rates, the important question studied in this experiment was the role of the glottic configuration in converting aerodynamic power to acoustic power, and the issue of whether subglottic pressure or airflow rate should be controlled for is irrelevant.

Before discussing the results, the use of an excised larynx preparation to study voice productions needs to be considered. In the excised larynges, metabolism stops when the blood supply ceases, the muscles cannot be activated by their motor nerves, and the organized structure of the tissues deteriorates gradually. It has been found that isolated larynges respond for a surprisingly long time (up to 1 month and more) in a reproducible way like the living larynx, provided they are preserved in a physiologic salt solution and refrigerated.[13] In our experiment, the larynges were studied immediately after excision, with the experiment completed within 3 hours from the time of excision. Furthermore, the consistency of the vibratory natures of the vocal folds in the excised canine model was confirmed by the reproducibility of the vibratory pattern as measured by F_0, jitter, shimmer, OQ, and SQ under specific test conditions repeated throughout the experiment (see Table).

Effect of Vocal Fold Tension. With maximal longitudinal tension on the vocal folds the cover of the vocal fold was tense and more elastic than at a lesser level of vocal fold tension. The vocal efficiency reached a maximum abruptly at a tension that produced modal vibration, and further increases in vocal fold tension led to a decrease in efficiency.

Stroboscopic video imaging during increased longitudinal vocal fold tension has demonstrated reduced lateral excursion of the vocal folds and reduced amplitude of the traveling wave.[14] We observed that as the vocal fold tension increased and the amplitude of the traveling wave diminished, the laryngeal efficiency of conversion of aerodynamic power to sound power decreased, while frequency of vibration continued to rise. Further increases in tension eventually led to replacement of the two-margin system by a high-frequency one-margin system above the modal voice register.

The changes in efficiency with changes in vocal fold tension were not related to changes in subglottic pressure and aerodynamic power. Rather, the changes in acoustic power produced by the changes in vocal fold vibratory pattern and the modulation of the airstream were responsible for the relationship of vocal fold tension to efficiency. The decreased amplitude of vibration with increased tension caused decreased modulation of the airstream and thus less acoustic power. Titze and Talkin,[15] using a model of tissue vibrations, reported that a slightly lax ligament provides freedom in the medial portion of the vocal folds to allow some vertical movement and vertical phase differences. However, a very tense ligament inhibited vertical movement and vertical phase differences. Vocal efficiency thus does not consistently increase with increasing tension.

Effect of Glottic Width. Width of the glottis is a key component to glottic competence and efficiency. The decrease in vocal efficiency for increased glottic width reflects the need to maintain a high flow of air with the wide glottis to induce vibration of the vocal folds via the Bernoulli effect. The patient with a wide glottis has air wastage with poor conversion of aerodynamic power to acoustic power.

As the glottic width decreased, the acoustic power radiated increased a greater proportion than the aerodynamic power supplied to the larynx. With decreased glottic width, the subglottic pressure increased, pushing the subglottic space upward and outward with greater extension of the glottic mucosa than for lower pressures.[16] Thus, with the decreased glottic width and increased subglottic pressure the vocal folds have been shown to have a greater amplitude of vibration.[16] An increase in amplitude of vocal fold vibration and aerodynamic power probably accounts for the increase in the acoustic power. The glottis received more aerodynamic power because of the decreased glottic width and also more efficiently converted the aerodynamic power to acoustic power because of the greater amplitude of vibration.

Titze[11] has reported that radiated acoustic power did not have any dependence on glottic width. However, subglottic pressure was kept constant during the experiment while glottic width was altered. Therefore, instead of observing an increase in subglottic pressure and a subsequent rise in acoustic power with a decrease in glottic width, by lowering the airflow rate to keep the subglottic pressure constant Titze found no change in acoustic power for the decrease in glottic width. This finding emphasizes the point that the changes in acoustic power seen with changes in glottic width in our experiment were due to changes in subglottic pressure.

In humans, subglottic pressure may be held constant during phonation by changing pulmonary effort and glottic configuration. Titze's[11] study kept subglottic pressure constant and observed that acoustic power was not altered as glottic width was changed. However, vocal efficiency was increased. For a smaller glottic width, the aerodynamic power was decreased, since the airflow had to be decreased to maintain a constant subglottic pressure; and there was thus a more efficient conversion of the lower aerodynamic power delivered to the larynx, maintaining a constant acoustic power.

The current study controlled for airflow rate as opposed to subglottic pressure and addressed the question of how the glottic configuration affects the efficiency of the larynx in converting aerodynamic power to acoustic power. As glottic width was decreased, vocal efficiency was found to increase, consistent with Titze's[11] results. Acoustic power increased when width decreased in this study because for a constant airflow rate, the subglottic pressure and aerodynamic power increased as the width narrowed. Titze[11] found no change in acoustic power when the glottic width was altered, because he kept subglottic pressure constant. Similarly, in this study for a decrease in glottic width, aerodynamic power increased because subglottic pressure increased as airflow stayed constant, while in Titze's study aerodynamic power decreased because subglottic pressure stayed constant as airflow was decreased to maintain a constant subglottic pressure as the glottic width decreased.

Although the two studies differ regarding whether airflow rate or subglottic pressure was kept constant, similar conclusions regarding the important question of how glottic configuration affects vocal efficiency were obtained from both experiments. An improved vocal efficiency with a decrease in glottic width can be concluded from both studies. However, one must be aware that extreme adduction and pressing of the vocal folds may have negative effects that can outweigh an improvement in efficiency.

Clinical Implications. Several laryngeal framework surgical procedures are being performed that alter the vocal fold tension and glottic width.[9,17] Arytenoid adduction narrows the glottic width, improving glottic competence and vocal efficiency. Extreme adduction must be avoided along with pressing of the vocal process, which may have deleterious effects. Alterations are made in the tension and length of the vocal folds in type II, III, and IV thyroplasties. The increased tension of the vocal folds with a type II or IV thyroplasty will increase F0, but excessive increases in tension may lead to a decrease in glottic efficiency if the vocal folds are tensed beyond the point of maximum efficiency. Stiffer vocal folds generally reduce the amplitude of vibration and thus can reduce acoustic power and vocal efficiency, whereas increasing subglottic pressure increases acoustic power and efficiency.

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CONFERENCE ON ASSISTIVE LISTENING DEVICES
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ENDOSCOPIC AND VIDEOFLUOROSCOPIC EVALUATIONS OF SWALLOWING AND ASPIRATION

SUSAN E. LANGMORE, PHD
ANN ARBOR, MICHIGAN

KENNETH SCHATZ, MA
YPSILANTI, MICHIGAN

NELS OLSON, MD
ANN ARBOR, MICHIGAN

A new procedure for evaluating oropharyngeal dysphagia utilizing fiberoptic laryngoscopy was compared to the videofluoroscopy procedure. Twenty-one subjects were given both examinations within a 48-hour period. Results of the fiberoptic endoscopic evaluation of swallowing (FEES) and videofluoroscopy examinations were compared for presence or absence of abnormal events. Good agreement was found, especially for the finding of aspiration (90% agreement). The FEES was then measured against the videofluoroscopy study for sensitivity, specificity, positive predictive value, and negative predictive value. Sensitivity was 0.88 or greater for three of the four parameters measured. Specificity was lower overall, but was still 0.92 for detection of aspiration. It was concluded that the FEES is a valid and valuable tool for evaluating oropharyngeal dysphagia. Some specific patients and conditions that lend themselves to this procedure are discussed.

KEY WORDS — aspiration, deglutition disorders, diagnosis, fiberoptics, instrumentation, pharynx, radiology.

INTRODUCTION

Otolaryngologists have become increasingly more involved in the diagnosis and treatment of patients with oropharyngeal dysphagia. When a patient's symptoms suggest difficulty with swallowing, the clinical examination will usually include indirect laryngoscopy or fiberoptic endoscopy. This is often followed by referral to radiologists and speech pathologists for a videofluoroscopic study, sometimes called the modified barium swallow study. This radiographic procedure has become the "gold standard" for assessment of oropharyngeal dysphagia, primarily because it provides information about bolus flow through the entire oropharynx, hypopharynx, and upper esophagus.

While the videofluoroscopic examination is an excellent procedure for imaging the dynamics of the swallow, there are many conditions that prevent the successful use of videofluoroscopy to evaluate dysphagia. Unavailability of fluoroscopy equipment on site may necessitate transfer of the patient to another facility for the study. Even when fluoroscopy is available, patients are regularly encountered in whom it cannot be used to assess dysphagia:

1. Patients who are in the intensive care unit and cannot easily be moved to the fluoroscopy suite.
2. Patients who are unable to be positioned adequately on the fluoroscopy platform or table because of severe weakness, limited mobility, or contractures.
3. Patients who are very ill and unable to tolerate the risk of aspirating even very small quantities of food.
4. Patients who need an immediate examination.

In order to adequately evaluate these patients at our medical center, the Speech Pathology and Otolaryngology Departments have jointly developed a technique that we call the fiberoptic endoscopic examination of swallowing (FEES). While the use of fiberoptic laryngoscopy to assess voice and to examine for structural abnormality or neuropathology[1-7] is well established, only a few investigators have described the use of this tool to directly assess swallowing function.[8-11] Several key events that characterize the abnormal swallow can be observed in this examination, the most important of which is aspiration, which signals that the patient may not be safe when eating and is at risk for pulmonary complications.

If the endoscopic examination is to be used as an alternative procedure to the videofluoroscopic study, its validity needs to be established. It is important to know whether endoscopy is as sensitive as fluoroscopy in detecting the major signs of oropharyngeal dysphagia, especially aspiration. Bastian[12] compared the results of double studies (endoscopic and videofluoroscopic) done on 10 subjects and found good agreement between the two examinations. In order to expand this preliminary work and help establish the validity of the FEES, the following investigation was carried out.

SUBJECTS AND PROCEDURE

Twenty-one subjects were studied. A wide variety of patients were included: 9 with a history of one or more cerebrovascular accidents, 5 with other

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From the Audiology and Speech Pathology Service, Department of Veterans Affairs Medical Center (Langmore, Olson), and the Department of Otolaryngology–Head and Neck Surgery, University of Michigan (Olson), Ann Arbor, and the Department of Communicative Disorders, Eastern Michigan University, Ypsilanti (Schatz), Michigan.

Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 2-3, 1990.

TABLE 1. INCIDENCE OF ABNORMAL FINDINGS ON TWO SWALLOWING EXAMINATIONS (N = 21)

	Abnormal(+) Findings		*Percent of Identical Findings on Both Examinations*
Event Scored	*Video-fluoroscopy*	*Fiberoptic Endoscopy*	*(Positive or Negative)*
Premature spillage	12	13	66
Pharyngeal residue	15	17	80
Laryngeal penetration	9	12	85
Tracheal aspiration	8	8	90

Positive findings on videofluoroscopy and fiberoptic endoscopic examination of swallowing did not necessarily occur in same subjects; thus percent agreement figure does not correspond directly to figures in first two columns.

neurologic disease, 2 with vocal cord paralysis, 2 with diagnoses of gastroesophageal reflux, 1 with a diagnosis of syncope, 1 post-coronary artery bypass graft, and 1 post-hemilaryngectomy. The mean subject age was 63, with a range of 35 to 94. All subjects were men. Subject selection depended solely on who could be given both dysphagia examinations within a short period of time.

The protocol for performing the FEES has been described in some detail elsewhere[9] but will be reviewed here briefly. Patients were examined in the clinic or at bedside in a posture typical of that in which they normally ate. The endoscope was passed transnasally to view the larynx and pharynx. Swallowing was directly evaluated with measured quantities of food and liquid dyed with blue food coloring for contrast. Two 5-mL swallows each of thin liquid, thick liquid, and applesauce and two small bites of bread were presented to each patient, always in that order.

The videofluoroscopic examination was conducted in the radiology suite, with the patient seated on a platform directly in front of the fluoroscopic unit. The same food and liquid consistencies and amounts as those used in the FEES were given to the patient. The food and liquid were mixed with barium powder to provide contrast.

The videofluoroscopy and FEES examinations were always completed within a 48-hour period, and usually within a 24-hour period. Four of the subjects had concurrent radiographic and endoscopic examinations. Examinations were scored by separate investigators, without knowledge of the results of the other examination. Each investigator performed an approximately equal number of FEES and videofluoroscopic examinations.

The occurrence of four abnormal features was scored in each examination: premature spillage, laryngeal penetration, tracheal aspiration, and pharyngeal residue. Laryngeal penetration was defined as material spilling into the laryngeal vestibule, but not passing below the vocal cords. Aspiration was defined as material falling below the glottis. This was observed either directly as the bolus fell between abducted vocal cords or after the swallow, as it rested on the subglottic "shelf" — the mucous membrane covering the lower part of the thyroid and cricoid cartilage, just below the anterior commissure. Alternatively, it could be observed as the patient coughed and expectorated green material that had been aspirated. Each event was scored as present (+) or absent (−) and a note was made as to the bolus consistency on which this event occurred. Findings for each subject on the two examinations were then summarized and submitted to statistical analysis to determine the extent of agreement between the two examinations.

RESULTS

All patients with one exception manifested one or more abnormalities on either or both of the swallowing examinations. Table 1 shows the incidence of abnormal findings on both examinations and the percentage of examinations that yielded identical findings on both examinations (either positive or negative findings). As seen in this Table, agreement was very high for three of the four parameters — aspiration (90%), penetration (85%), and residue (80%) — hence, findings on one examination tended to agree with findings on the other. However, it should be noted that less than 50% of the examinations (9 of 21) were in total agreement with regard to all four parameters that were scored for each patient.

The FEES was measured against the videofluoroscopic study for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Calculations for these statistics were taken from Browner et al[13] and were defined as follows: *sensitivity* — the proportion of positive findings on videofluoroscopy that yielded a positive result on the FEES = a true positive/(true positive + false negative); *specificity* — the proportion of negative findings on videofluoroscopy that yielded a negative result on the FEES = true negative/(true negative + false positive); *positive predictive value* — the probability that the subject with a positive finding on the FEES actually had that abnormality (on videofluoroscopy); *negative predictive value* — the probability that the subject with a negative finding on the FEES did not actually have that abnormality (on videofluoroscopy). The values obtained for these statistics are shown in Tables 2 and 3. The FEES was highly sensitive (0.88 or greater) for residue, penetration, and aspiration, indicating that nearly all instances of these abnormalities detected on the videofluoroscopic study were also detected on the FEES. Sensitivity for premature spillage was somewhat lower, suggesting that some instances of spillage on the fluoroscopy study were not observed during the FEES. Specificity, a measure of the ability of the test to correctly detect true negatives, was not quite as high for pre-

TABLE 2. SENSITIVITY AND SPECIFICITY VALUES FOR RESULTS OF FIBEROPTIC ENDOSCOPIC EXAMINATION OF SWALLOWING WHEN COMPARED TO FINDINGS ON VIDEOFLUOROSCOPY (N = 21)

Event Scored	*Sensitivity*	*Specificity*
Premature spillage	0.75 (0.55-0.87)*	0.56 (0.47-0.63)*
Pharyngeal residue	0.93 (0.74-0.99)	0.50 (0.38-0.62)
Laryngeal penetration	1.00 (0.75-1.1)	0.75 (0.55-0.87)
Tracheal aspiration	0.88 (0.63-1.01)	0.92 (0.72-1.0)

*95% confidence intervals.

TABLE 3. ABILITY OF FIBEROPTIC ENDOSCOPIC EXAMINATION OF SWALLOWING TO CORRECTLY PREDICT "TRUE" FINDINGS AS SEEN ON VIDEOFLUOROSCOPY (N = 21)

	PPV of FEES	*NPV of FEES*
Premature spillage	0.69 (0.46-0.86)*	0.63 (0.43-0.79)*
Pharyngeal residue	0.82 (0.57-0.97)	0.75 (0.55-0.87)
Laryngeal penetration	0.75 (0.55-0.87)	1.00 (0.75-1.12)
Tracheal aspiration	0.88 (0.63-1.01)	0.92 (0.72-1.0)

PPV — positive predictive value, FEES — fiberoptic endoscopic examination of swallowing, NPV — negative predictive value.
*95% confidence intervals.

mature spillage and pharyngeal residue as the other two parameters, suggesting that videofluoroscopy sometimes yielded a negative finding when the FEES yielded a positive finding. However, specificity was very high for laryngeal penetration and aspiration (0.75 and 0.92, respectively), indicating that negative findings for these parameters on videofluoroscopy usually yielded negative findings on the FEES as well.

Positive and negative predictive values, shown in Table 3, indicate the ability of FEES to correctly predict the "true" findings as seen on videofluoroscopy. The PPV and NPV were 0.75 or higher for three of the four parameters, with premature spillage being somewhat less predictable. Laryngeal penetration yielded an NPV of 1.00, since all negative findings on the FEES were also observed on videofluoroscopy. Aspiration yielded figures of 0.88 and 0.92, with 7 of the 8 positive results and 12 of the 13 negative results on the FEES also observed on videofluoroscopy. (The PPV and NPV take the prevalence of findings on the "standard" examination into account, thus accounting for the higher NPV than PPV on this parameter.)

In this study, the occurrence of specific abnormalities according to consistency of bolus (thick liquid, pureed, etc) was not submitted to statistical analysis, since the numbers would have been too low to perform any meaningful analyses. However, a perusal of the data indicated that the two examinations usually agreed with each other regarding bolus consistency involved in the abnormal event. There was no discernible tendency for either examination to detect aspiration or penetration of any particular consistency with greater frequency.

DISCUSSION

In this study, the FEES was compared to the videofluoroscopic study, and it proved to be a reliable procedure for detecting some of the major symptoms of dysphagia in the pharyngeal stage. All cases of laryngeal penetration, and all but one case of aspiration and residue on the videofluoroscopic study, were also reported positive on the FEES. Sensitivity and specificity, which give an indication of the number of "true" positive and "true" negative results when compared to the "gold standard," were best for aspiration and penetration, and somewhat lower for the other parameters. In general, a finding of penetration or aspiration on the FEES had few false-positive or false-negative results.

Positive and negative predictive values are often used to indicate the clinical usefulness of an examination.[14] In this study, the FEES was found to be a good predictor of a patient's "true status" (as determined by videofluoroscopy) for three of the four parameters. The only parameter with relatively low predictive values (0.70) was premature spillage. The fact that neither the FEES nor the radiographic examination reported a higher number of positive or negative findings suggests that the variability may lie within the patient. The level of variability reported in this study compares favorably to that in other studies that have looked at this issue. Using videofluoroscopy, Lof and Robbins[15] reported that normal subjects showed variability in swallowing performance from one trial to the next and with repeated studies, although the differences in performance were not significant. Similarly, Ekberg et al[14] reported interobserver variability in raters' judgments of findings on fluoroscopic studies, although they concluded that the level of disagreement was "acceptable." Hence, there are several possible sources of the variability we found between the FEES and videofluoroscopic studies, including patient variability, rater variability, and differences between the procedures.

Even though the endoscopic study was shown to be a sensitive procedure for detecting aspiration, penetration, and pharyngeal residue, we are not suggesting that the FEES replace videofluoroscopy as the "gold standard." Videofluoroscopy remains the most thorough diagnostic tool available today for evaluating oral-pharyngeal dysphagia. Precise measurements of oral and pharyngeal transit times, and direction and amplitude of movement of structures, can only be done at present with fluoroscopic images.

However, we do believe that the FEES is a valuable tool in the evaluation of the dysphagic patient. With videotape recording and slow playback capabilities, FEES can reveal much about bolus flow through the hypopharynx, movement of the structures in reaction to or anticipation of the bolus, and sensitivity within the hypopharynx and endolarynx. It is possible to visualize and localize residual material within the hypopharynx or larynx better endoscopically than with the two-dimensional view afforded by videofluoroscopy, and this information can be very revealing.[16] Finally, an assessment of airway protection with maneuvers such as holding the breath, coughing, and clearing secretions can only be done adequately with endoscopy.

In addition, the endoscopic examination has practical advantages over the fluoroscopic examination. The FEES is performed with a tool already available to otolaryngologists and can be easily added to a routine flexible laryngoscopic examination whenever the patient's complaints suggest dysphagia. It is also a portable examination; it can be brought to bedside or done in the office and does not require the extensive effort and expense involved when occupying a radiographic suite with a radiologist, a technologist, and a speech pathologist. It can be repeated as often as desired without undue radiation hazard to the patient.

As an initial examination, FEES can tell the examiner whether a pharyngeal dysphagia is present and whether the problem includes clinical symptoms such as aspiration, laryngeal penetration, or excess residue. It can also reveal clinically significant abnormalities such as incomplete vocal cord adduction. If a speech pathologist participates in the examination, more detailed considerations regarding safety of oral feeding, appropriate diet, need for behavioral therapy, and the usefulness of a follow-up videofluoroscopic study can be made (for example, see Logemann[17]). More research is needed with larger samples participating in combined studies in order to sort out the factors accounting for the observed variability and to further investigate the sensitivity of each examination with different food consistencies. However, this study has established that endoscopy is a valid and valuable tool for evaluating oropharyngeal dysphagia.

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IMAGING CASE STUDY OF THE MONTH

SEPTIC JUGULAR THROMBOSIS WITH ABSCESS FORMATION

FERIT TOVI, MD
ALBERT GATOT, MD
DAN M. FLISS, MD
YANCU HERTZANU, MD
BEER-SHEVA, ISRAEL

PATIENT

A 10-year-old boy was referred with a fluctuating mass in his right upper neck. According to his medical history, at 3 years of age he had undergone a right ventricular-atrial shunt because of hydrocephalus. Four years later, because of dysfunction of the shunt, he underwent a similar procedure on the left side. At the present admission he was first seen in the pediatric department, tapping of the cervical mass yielded 10 mL of gas, and the swelling disappeared. Twenty-four hours later the lesion recurred. On admission to the otolaryngology department he was febrile (40°C) and tachycardiac (120 pulses per minute). A nonerythematous, tender, fluctuating mass 6 cm in diameter was palpated in the right upper neck. The findings of the rest of the examination were normal. A routine blood count showed a leukocytosis of 15,000 mm/cm with a shift to the left and a hemoglobin of 7 g/dL. The erythrocyte sedimentation rate was 50 mm/h in the first hour. The chest radiographic findings were normal. Radiographic studies of the neck showed the presence of bilateral shunt catheters. On the right side, the tip of the catheter projected at the level of the lower neck. Contrast pharyngography showed no pharyngeal-cervical communication. Postcontrast computed tomography (CT) of the neck revealed a well-defined mass with surrounding enhancing rim in the location of the jugular vein (see Figure, A). A fluid gas level was obvious within the confines of this lesion (see Figure; B,C). Because of septic fever, intravenous antibiotic therapy of crystalline penicillin (8,000,000 U) and chloramphenicol (Synthomycetine, 1 g) was initiated, and exploration of the neck was indicated.

At the operation, the right shunt was centrally disconnected through a retroauricular incision and the cranial bur hole was sealed by a temporal muscle flap. Subsequently, the cervical mass was approached by a longitudinal incision along the anterior border of the sternocleidomastoid muscle. In the medial aspect of the muscle, a cystic structure was detected that had firm adhesions to the surrounding tissues, including the common carotid artery. At dissection, the mass was found extending from the jugular fossa to the thoracic inlet. Because of the anatomic course and the presence of the catheter within its confines, it was considered to be a thrombosed internal jugular vein. The lesion was totally excised.

In the early postoperative period the patient remained febrile. By the fourth postoperative day his general condition gradually ameliorated and he remained symptom-free a week after the operation. Cultures from the cystic content yielded no growth. In gross examination of the specimen, the mass showed a tubular structure with central cystic dilatation. Cut sections at the cyst level showed a thick-walled structure surrounding a cavity filled with yellowish fluid that contained bubbles. Distal to the cyst, in both directions, the structure presented as a solid cord. Histologic findings were compatible with a severely inflamed venous channel with abscess formation and thrombosis.

DISCUSSION

Thrombosis of the jugular vein may occur by direct tumor infiltration, tumoral emboli, compression by a local neoplasm, distal extension of a dural sinus thrombosis, surgical manipulation, direct injection to the vein, venous catheterization for various purposes including cerebrospinal fluid shunting, or a local or regional septic process.[1-4] The last condition was frequently encountered in the preantibiotic era and was associated with fascial space infections of the head and neck.[5] Today, septic thrombophlebitis is rarely diagnosed, mainly because of placement of central venous catheters.[5] Less frequently, intravenous drug abuse[6,7] and postanginal sepsis were also described in the causation of the disease.[8,9] Septic jugular thrombosis is a potentially life-threatening condition, since it carries the risk of distal embolization and results in pulmonary embolism, septicemia, and sometimes septic involvement of other peripheral organs.[8,9]

The morphologic feature of septic thrombosis of the jugular vein is partial or total occlusion of the lumen with an infected thrombus and infectious inflammatory changes in the vessel walls.[10,11] Occa-

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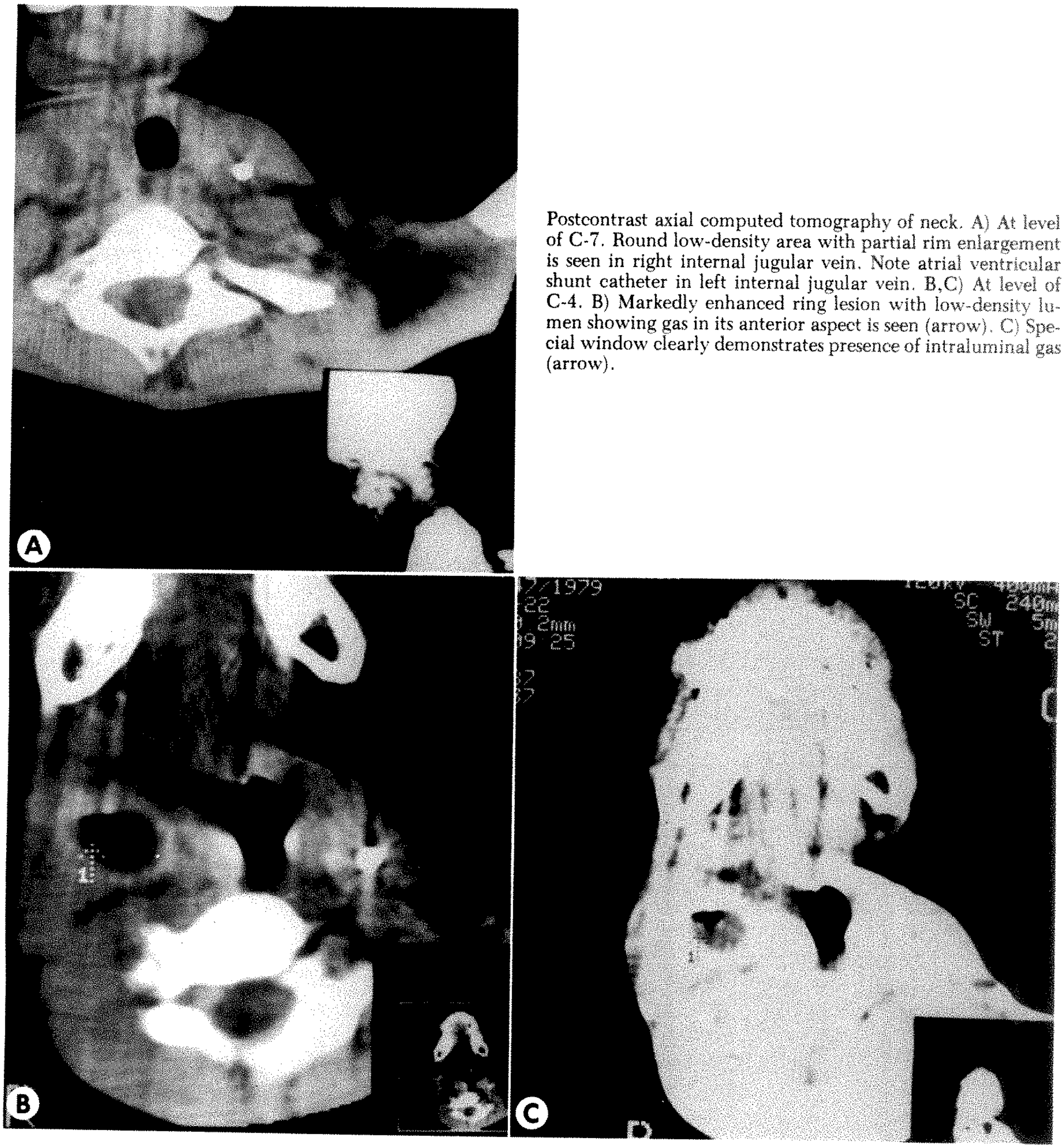
From the Otolaryngology and Head and Neck Department (Tovi, Fliss, Gatot) and the Radiological Institute (Hertzanu), Soroka University Hospital, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.



Postcontrast axial computed tomography of neck. A) At level of C-7. Round low-density area with partial rim enlargement is seen in right internal jugular vein. Note atrial ventricular shunt catheter in left internal jugular vein. B,C) At level of C-4. B) Markedly enhanced ring lesion with low-density lumen showing gas in its anterior aspect is seen (arrow). C) Special window clearly demonstrates presence of intraluminal gas (arrow).

sionally, necrosis and perforation of the vessel may occur. Concomitant inflammation or abscess formation in the adjacent soft tissue has been described.[7] Intraluminal, frank abscess formation is an unusual feature of septic thrombosis of the jugular vein, and to the best of our knowledge, although clinically reported,[9] it has not been radiographically documented. Computed tomography has proved to be a noninvasive, accurate diagnostic imaging modality for the evaluation of the patency of the vascular structures. There is a universal agreement that contrast enhancement is critical in evaluating the pattern of the vascular channels. The features of venous thrombosis seen by CT were described by Zerhouni et al[12] and include dilatation of the thrombosed vein, a hypolucent lumen, and a sharply defined, dense wall. However, in the early developmental stages the thrombus may appear as dense as the contrast-enhanced blood. On CT, it is difficult to differentiate between septic and tumoral occlusion of the venous channels unless an intraluminal abscess is demonstrated.[9]

In the presented case the CT finding of an air-fluid level within the confines of the internal jugular vein exclusively indicated a septic process associated with abscess formation. Additionally, soft tissue swelling adjacent to the thrombosed jugular vein was also suggestive of an infectious inflammatory process. The long-standing catheterization of the jugular vein for shunting purposes was complicated by thrombosis of this venous channel. Patients with cerebrospinal fluid shunts are prone to complications — mainly obstruction and infection. In our case, the tip of the catheter was found to project at the level of the lower neck instead of being localized in the right atrium.

Atrial shunts necessitate annual radiographic studies in order to confirm the location of the catheter tip, which changes according to the axial growth of the subject.[13] Most probably, the mislocated catheter tip traumatizing the venous endothelium initiated the process of thrombosis of the internal jugular vein. The occurrence of an abscess can be explained by an occasional blood-borne infection that contaminated the already thrombosed vein.

The therapeutic approach to septic thrombophlebitis secondary to venous catheterization is based on the removal of the catheter and appropriate antibiotic therapy.[9,14] But in cases of abscess formation, operative intervention is mandatory.[14-16] Otherwise, a conservative regimen will result in a protracted course of the disease, with occurrence of distal septic complications.

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MEDICAL CONSULTATION AND MANAGEMENT IN THE PERIOPERATIVE PERIOD

A course, Medical Consultation and Management in the Perioperative Period, will be given October 4-5, 1991, at the Sheraton Inner Harbor Hotel, Baltimore, Maryland. This course is sponsored by the Division of General Internal Medicine and Geriatrics, University of Maryland School of Medicine, Baltimore. For information, please contact Ms Lorraine Zaganas, N3W129, University Hospital, 22 S Greene Street, Baltimore, MD 21201; (301) 328-6598.

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IMAGING CASE STUDY OF THE MONTH

CEREBELLOPONTINE ANGLE METASTATIC LUNG CARCINOMA RESEMBLING AN ACOUSTIC NEUROMA

DAVID R. NELSON, MD   KENNETH D. DOLAN, MD

IOWA CITY, IOWA

INTRODUCTION

Temporal bone metastatic tumors are more common than is recognized. Most of these tumors are microscopic and therefore asymptomatic.[1] Small cell carcinoma of the lung frequently metastasizes widely, with typical involvement of the liver, adrenals, and kidneys. Solid metastases to the brain parenchyma occur in approximately 20% of cases.[2,3] Temporal bone metastases are less common, and involvement of the meninges in the cerebellopontine angle (CPA) without temporal bone involvement is even more rare.[4] Recently, magnetic resonance imaging using the intravenous contrast agent gadolinium–diethylenetriamine pentaacetic acid (Gd-DTPA) has been shown to be the imaging modality of choice for evaluation of patients with suspected CPA masses.[5,6]

CASE REPORT

A 67-year-old man with a 2-year history of small cell carcinoma of the lung presented with rapidly progressive hearing loss in the left ear and unsteadiness without vertigo. The patient had known metastases to the liver and choroid of the left eye and had been treated with cisplatin and Cytoxan, Adriamycin, and vincristine. He was felt to be in complete remission at the time of his sudden hearing loss. At that time, physical examination revealed the Weber test to lateralize to the right, left sensorineural hearing loss, and poor tandem gait. An enhanced computed tomographic scan of the head showed no evidence of metastatic disease (Fig 1). The patient returned 3 weeks later and magnetic resonance examination with and without Gd-DTPA was performed (Fig 2). T1-weighted images were obtained in the axial and coronal planes of the posterior fossa. T2-weighted axial images were obtained of the whole brain; then axial and coronal T1-weighted images of the posterior fossa were obtained after intravenous administration of Gd-DTPA (0.1 mmol/kg). Figure 2A shows enlargement of the left intracanalicular nerve trunk with a 1.5-cm CPA mass. The intracanalicular and CPA masses enhance with contrast material in Fig 2B. A view 3 mm below that in Fig 2B shows three other enhanced meningeal masses, as well as a small vermis metastasis (Fig 2C).

DISCUSSION

Meningeal carcinomatosis involving the CPA in bronchogenic carcinoma is uncommon, and to the authors' knowledge, fewer than 10 cases have been reported.[1,3] Characteristic symptoms of meningeal carcinomatosis with involvement of the CPA and internal auditory canal include tinnitus, rapidly progressive or sudden unilateral or bilateral sensorineural hearing loss, and loss of vestibular function. Facial paralysis, which is progressive, is a common finding with metastases to the temporal bone and has also been reported in several cases of meningeal involvement in the region of the internal auditory canal.[1,3] Our patient presented with the typical findings of eighth nerve involvement without involvement of cranial nerve VII.

The mechanism of spread to the temporal bone

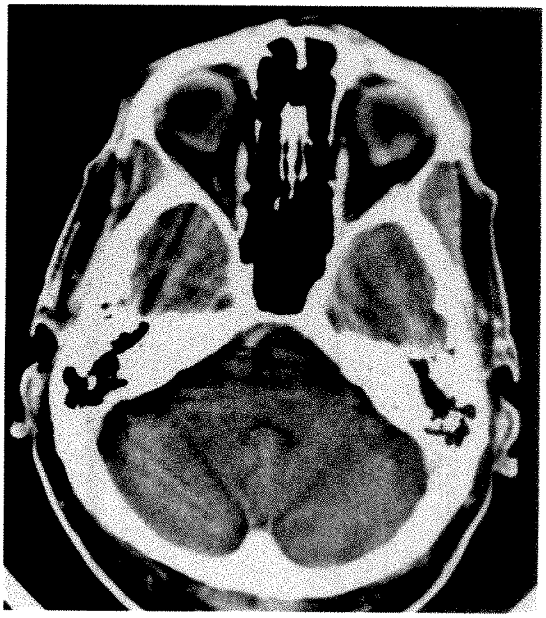

Fig 1. Enhanced computed tomogram at level of internal canals shows no abnormality.

From the Department of Radiology, The University of Iowa School of Medicine, Iowa City, Iowa.

REPRINTS — Kenneth D. Dolan, MD, Dept of Radiology, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

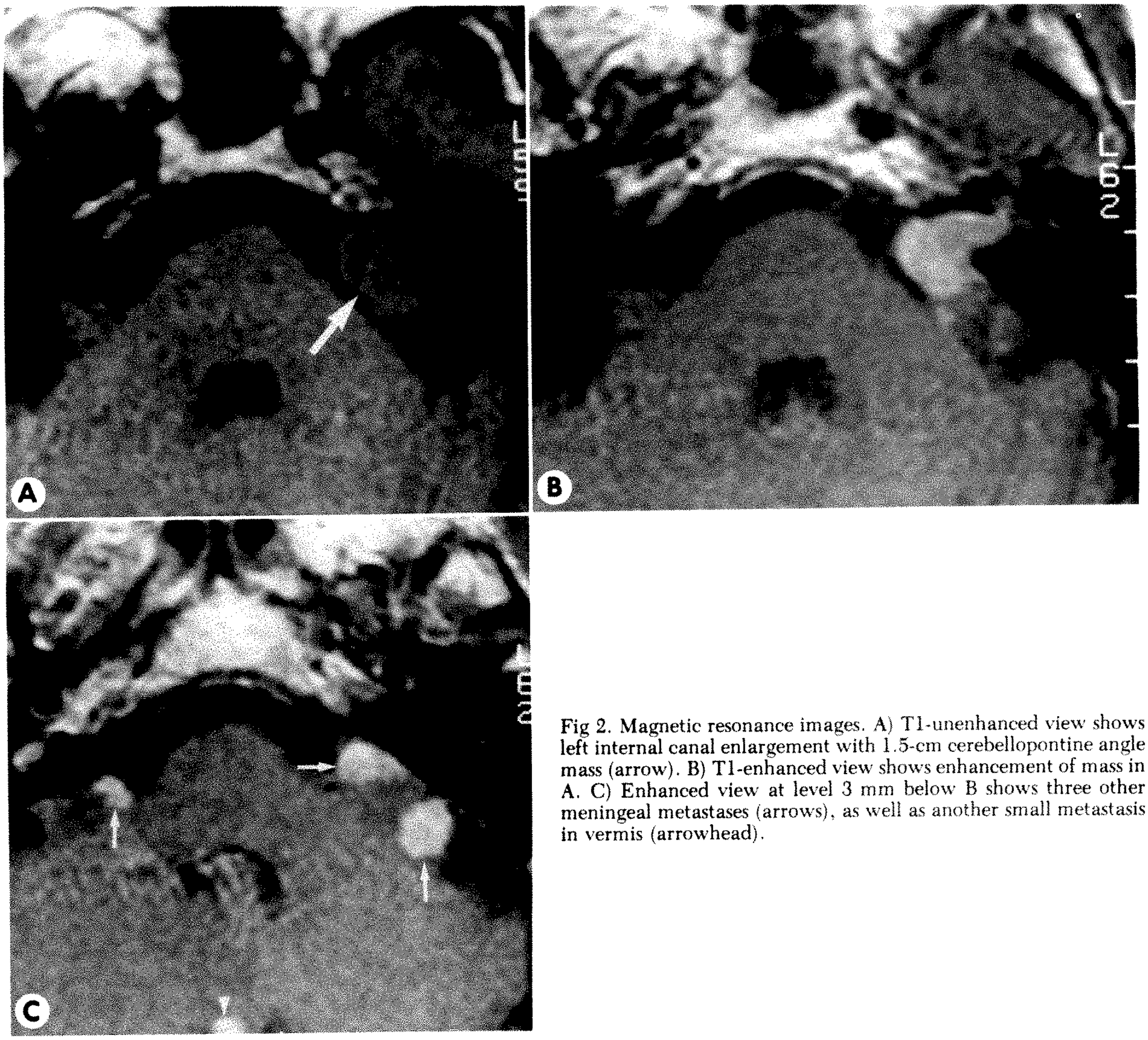

Fig 2. Magnetic resonance images. A) T1-unenhanced view shows left internal canal enlargement with 1.5-cm cerebellopontine angle mass (arrow). B) T1-enhanced view shows enhancement of mass in A. C) Enhanced view at level 3 mm below B shows three other meningeal metastases (arrows), as well as another small metastasis in vermis (arrowhead).

appears to usually involve a hematogenous route.[7] Tumor cells carried by the pulmonary veins to the heart and systemic circulation result in parenchymal brain or bony involvement. An alternate route, involving dissemination of tumor cells by the paravertebral venous plexus, could result in meningeal carcinomatosis. Our case shows evidence of both types of spread, since there were solid intraparenchymal lesions as well as bilateral meningeal involvement. This case also demonstrates the usefulness of Gd-DTPA–enhanced magnetic resonance images in evaluating suspected CPA masses.

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PATHOLOGY CONSULTATION

BASALOID MONOMORPHIC ADENOMAS

JOHN G. BATSAKIS, MD
MARIO A. LUNA, MD
ADEL K. EL-NAGGAR, MD, PHD
HOUSTON, TEXAS

Monomorphic adenomas can be divided into basaloid and nonbasaloid types. With the exception of the canalicular adenoma, the basaloid monomorphic adenomas are preponderantly tumors of the major salivary glands, most often the parotid gland. The dermal analogue monomorphic adenomas, so named because of their histologic similarity to eccrine tumors of the skin, are a unique subset of the basaloid adenomas. They are often multifocal, recur frequently, may undergo malignant change, and can be part of a salivary-cutaneous tumor diathesis.

Monomorphic adenomas were separated as a class of salivary gland neoplasms in 1967.[1] Since then a variety of well-known as well as lesser-known entities have been placed under the rubric of monomorphic adenoma.[2-4] Among the former are Warthin's tumor, oncocytoma, and sebaceous lymphadenoma. The others are a collection of tumors that are primarily characterized by hyperchromatic, usually uniform basaloid cells arranged in several growth patterns (Table 1). "Basal cell" adenoma and basaloid monomorphic adenoma are the most widely used terms for this subset of monomorphic adenomas.[4-6]

Given the breadth of histologic expression manifested by monomorphic adenomas, it is difficult to collectively define these tumors. Cho and Kim[7] give us one of the best definitions. In a broad context, monomorphic adenomas are almost all of the benign salivary gland tumors, exclusive of pleomorphic adenoma. The more narrow definition of monomorphic adenoma is a salivary gland tumor, devoid of a myxoid or chondroid stromal matrix, that shows a distinct epithelial basement membrane.

The nonbasaloid monomorphic adenomas are quite stereotypic (eg, Warthin's tumor, oncocytoma, ductal adenoma) and consequently only infrequently pose problems in classification. It is with the basaloid monomorphic adenomas that arguments over nomenclature,[8] histogenesis,[4,9] and subclassification[4,5,10] persist. It is also this group that continues to pose problems in differential diagnosis for surgical pathologists.

Basaloid monomorphic adenomas segregate into three subtypes: canalicular, dermal analogue, and tubulotrabecular-solid.[4] Canalicular adenomas are almost exclusively intraoral and are preponderantly labial in site of origin. The major salivary glands, particularly the parotid, host the others. A recent Pathology Consultation has discussed the canalicular monomorphic adenoma.[11] The present report concentrates on the noncanalicular monomorphic adenomas.

Tubulotrabecular (see Figure, A) and solid monomorphic adenomas are the monomorphic adenomas most closely related to the pleomorphic adenomas. The relationship is histogenetic, phenotypic, and clinical. It is likely that the principal difference between them and pleomorphic adenomas is the myoepithelial cell and its evocations on the stromal components.[7] The Figure (B) illustrates this effect wherein the ductal monomorphic adenoma (see Figure, C) and myoepithelioma are at the poles of a continuum linking these forms of monomorphic adenomas and pleomorphic adenoma. Recognition of the spectrum of myoepithelial cell–controlled phenotypes should eliminate nosologic confusion perpetuated by terms such as "basal cell adenoma with myoepithelial cell-derived 'stroma,'"[10] which describes no more than a stroma-poor pleomorphic adenoma.

Some of the tubulotrabecular and solid forms of monomorphic adenoma bear a histologic similarity to adnexal tumors of the skin, but it is the dermal analogue or dermal-type monomorphic adenoma in which the similarity is most striking.[4,12-15] The influence of myoepithelium is less in these tumors, and the analogous relationship with adnexal tumors along with a distinctly different biologic behavior (Table 2[6,14,15]) clearly distinguishes the dermal ana-

TABLE 1. CLASSIFICATION OF MONOMORPHIC ADENOMAS

Basaloid Adenomas	*Nonbasaloid Adenomas*
Tubulotrabecular	Warthin's tumor
Solid	Oncocytoma
Canalicular	Sebaceous lymphadenoma
Dermal analogue	Sebaceous
	Ductal (mucinous, nonmucinous, epidermoid)

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

TABLE 2. BASALOID MONOMORPHIC ADENOMAS

	*Dermal Analogue Type**	*Other Types*
Number of patients	25	102
Sex of patients (M/F ratio)	10/1	1/1
Age at diagnosis	34 to 74 y (mean, 58.1 y)	Neonate to 83 y (mean, 58.6 y)
Number of patients with synchronous dermal appendage tumors	9 (37.7%)	0
Salivary gland site		
Parotid	25	92
Submandibular	2	5
Upper lip	0	5
Nasal cavity	1	0
Hypopharynx (?)	1	0
Multicentric salivary gland involvement	12 (48%)	1
Size of adenoma	1.5 to 4.5 cm (mean, 3.4 cm)	1.5 to 4.0 cm (mean, 2.6 cm)
Number of patients with recurrences	6 (24%)	0
Malignant "transformation"	7 (28%)	4 (3.9%)

Data collected from Mintz et al,[6] Luna et al,[14] and Daley et al.[15]

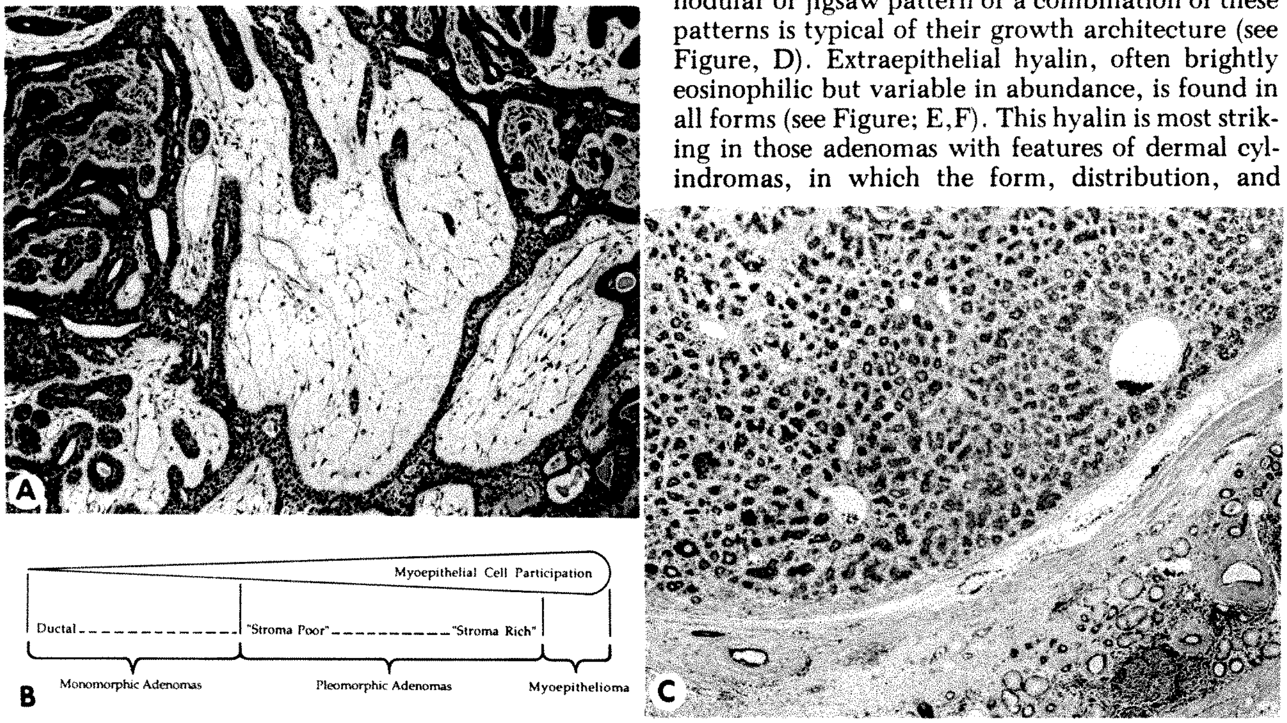
*Twenty-five patients with dermal analogue monomorphic adenomas had 29 tumors.

logue tumors from the other types of basaloid monomorphic adenomas.

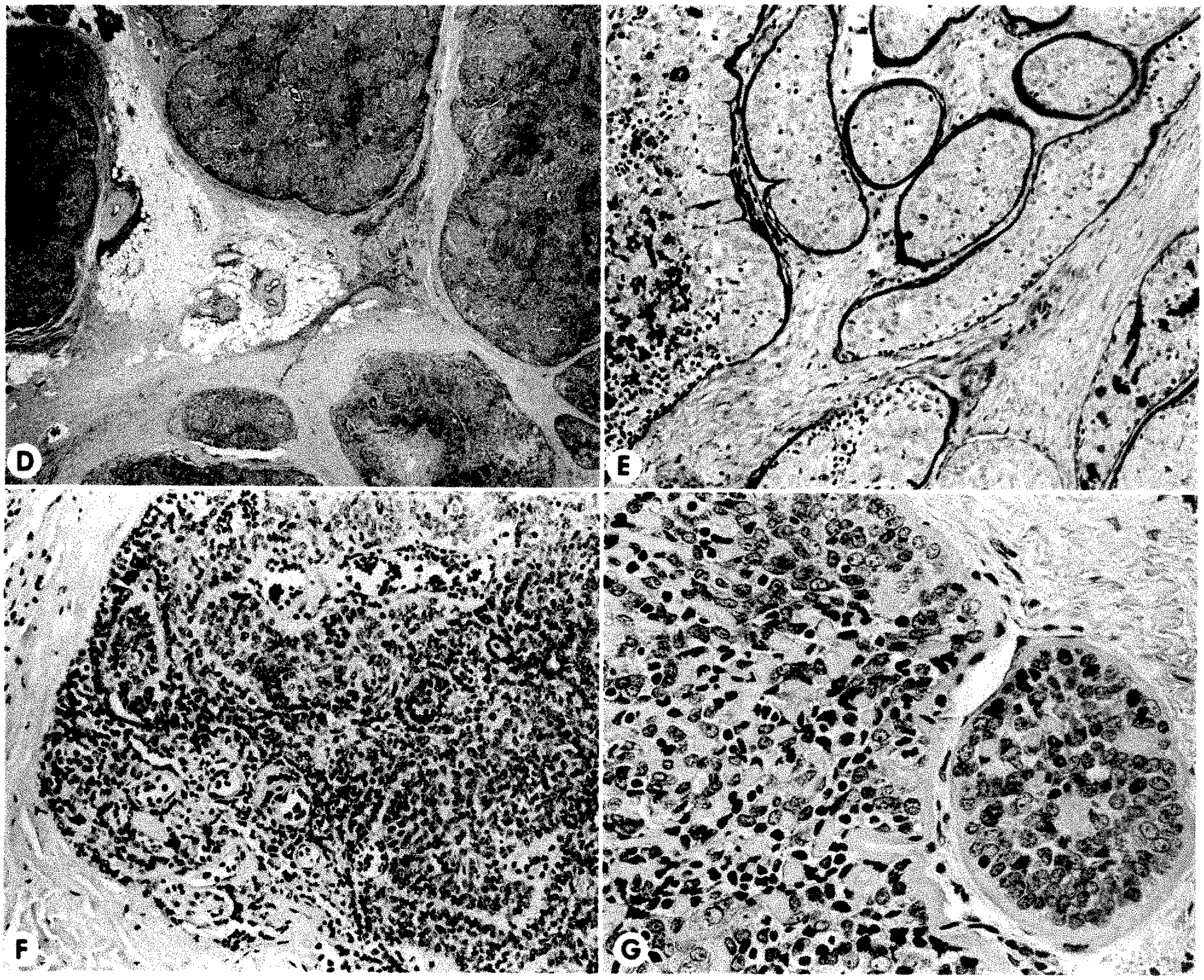
Dermal analogue adenomas manifest a male predilection, are often multicentric, have a respectable recurrence rate (perhaps because of this multicentricity), and are the monomorphic adenomas most often associated with malignant transformation to malignant basaloid tumors or basaloid carcinomas.[16] They are also singular in that they are the only type of monomorphic adenoma with synchronous cutaneous dermal appendage tumors, eg, dermal cylindroma, eccrine spiradenoma.[12,13,17-19] Like Warthin's tumors, the dermal analogue tumors can also arise from intranodal salivary tissues.[14]

There is no doubt the dermal analogue monomorphic adenomas represent a separate nosologic entity. Representing about 10% of all monomorphic adenomas, their distinctive histologic appearance and the salivary-dermal tumor diathesis with which they are uniquely associated serve to single them out from other adenomas. The cutaneous tumors have been eccrine or trichoepithelial in derivation and have been multiple. One of our patients had over 1,000 skin lesions in association with his dermal analogue tumor of the parotid gland. Although multiple dermal cylindromas are inherited as an autosomal dominant trait, there has not yet been noted a familial tendency with the salivary gland analogues.[17,19]

Except for those arising within parotid area lymph nodes, the dermal analogue monomorphic adenomas are not usually encapsulated. Indeed, as Headington et al[13] showed, their origin is multifocal. The multifocality may be retained or obscured by coalescence at the time of surgical removal. A micronodular or jigsaw pattern or a combination of these patterns is typical of their growth architecture (see Figure, D). Extraepithelial hyalin, often brightly eosinophilic but variable in abundance, is found in all forms (see Figure; E,F). This hyalin is most striking in those adenomas with features of dermal cylindromas, in which the form, distribution, and



Monomorphic adenomas. A) Basaloid monomorphic adenoma of parotid gland with tubulotrabecular growth pattern (H & E, original x80). Note characteristic delicate vasculature in delicate reticular stroma. B) Influence of myoepithelial cell participation in phenotypic expression seen in spectrum of monomorphic and pleomorphic adenomas. There appears to be continuum rather than sharp distinction between basaloid monomorphic adenomas and pleomorphic adenomas. C) Ductal adenoma of intraoral minor salivary gland (H & E, original x80). Perhaps least common of monomorphic adenomas, it has little or no myoepithelial contribution. (Continued on next page.)



D-F) Dermal analogue monomorphic adenomas of parotid gland. D) Note multifocal nature of this tumor that resembles eccrine spiradenoma of skin (H & E, original x40). E) Stained with periodic acid-Schiff reagent to highlight replicated basement membranes outlining epithelial islands (original x80). F) Eosinophilic hyalin-type material is perivascular, around epithelial nests and in small interepithelial droplets (H & E, original x160). G) Dermal cylindroma type of monomorphic adenoma (H & E, original x160). Its distinctive basaloid cells and eosinophilic hyalin-type material are nearly identical to those of analogous tumor of skin.

amount of the hyalin is identical with that of the dermal eccrine tumor (see Figure, G).

The dermal cylindroma type of monomorphic adenoma also shares with its cutaneous counterpart an infiltrative appearance; hence, that feature cannot be used to separate benign from malignant tumors.[20] Small nerve encroachment, but not invasion, can be seen in the dermal analogue monomorphic adenomas.[4,12] Spontaneous necrosis of the epithelial islands is foreign to the monomorphic adenoma. If this necrosis is present, suspicion for advent of malignant change is heightened and other findings such as mitotic activity, loss of polarity of cells, and nuclear and cytoplasmic pleomorphism and polymorphism should be sought.

The major differential diagnosis is an adenoid cystic carcinoma. A dearth of tubular differentiation, an absence of cribriform architecture, and a maintenance of peripheral palisading of cells in the monomorphic adenoma, along with the resemblance to cutaneous adnexal tumors, serve to distinguish the adenoma from the carcinoma.

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PATHOLOGY CONSULTATION

SALIVARY-TYPE NEOPLASMS OF THE SINONASAL TRACT

JOHN T. MANNING, MD JOHN G. BATSAKIS, MD

HOUSTON, TEXAS

Salivary-type neoplasms of the nasal cavity and paranasal sinuses are numerically dominated by adenoid cystic carcinomas and pleomorphic adenomas. All others, benign or malignant, are rarely encountered and are usually biologically and histologically low-grade. Sites of origin in the sinonasal tract conform to the density and distribution of the seromucous glands and hence are most often nasal (septum and turbinates) or ostial.

Glandular neoplasms of the sinonasal tract can be imperfectly separated into two groups: those with an unequivocal origin from the surface epithelium and those with histologic phenotypes analogous to those of salivary neoplasms found in the major salivary glands or oral cavity. In numbers of reported cases, except for adenoid cystic carcinomas, the former exceed the latter by a considerable margin.[1-3]

One of the reasons for the imperfect separation of the two groups is that the submucosal glands are direct invaginations of the surface (luminal) epithelium and are, in the main, not "accessory salivary-type" glands.[4] Kleinsasser,[5] in his discussion of the seromucous glands of the nasal respiratory mucosa or "glandulae nasales," describes them as irregularly branching tubules that often end blindly and occasionally terminate in a slight distention, the acinus (see Figure, A). Many of the glands, particularly in the paranasal sinuses, do not manifest the structural subdivisions of the major salivary glands into acinus, intercalated ducts, and striated ducts. Terminal-type ducts appear to merge directly into tubular demilunes. Myoepithelial cells also have not been consistently identified in normal sinonasal seromucous glands.

Pertinent also to the localization and frequency of salivary-type glandular neoplasms in the nasal cavity and paranasal sinuses are the distribution, density, and location of the submucosal glands. Compared to those in the nasal cavity, sinus seromucous glands are fewer and manifest less secretory activity. They have their greatest concentrations close to the ostia. Indeed, except for these small zones, there is no definable glandular layer in the paranasal sinuses.[1] The few glands are scattered singly amid large areas devoid of seromucinous glands. Glandular density, considered on the basis of an entire sinus, is highest in the ethmoids and lowest in the frontal sinus. The actual number of glands in the paranasal sinus is small: fewer than 50 in the frontal and sphenoid sinuses and 50 to 100 in the ethmoids.[1] These numbers are in great contrast with those in the nasal cavity, in which there is a gland density of 7 to 10 glands per square millimeter and about 36,000 glands on the nasal septum and middle and inferior turbinates.[1] In the nasopharynx and at the oral end of the eustachian tube in the superior surface of the soft palate there is an equally high concentration of glands.[6] In summary, the density of seromucous glands decreases in the following order: septum and turbinates, ostial antrum, ethmoids, frontal sinus, and sphenoid sinus. Glands are notably sparse in the last two sinuses (see Figure, B) and they are absent in a 1.5-cm area just above and behind the nasal vestibule.[6]

The aforestated distribution and density of subsurface seromucous glands coincide with the usual sites of origin of sinonasal salivary-type neoplasms, ie, septum, turbinates, and ostia. Except for adenoid cystic carcinoma, however, there is little in the literature to build a clinicopathologic prospectus for salivary-type neoplasms in the sinonasal tract other than to underscore their relative rarity. Tables 1[7] and 2,[8] prepared from data in two overview reports and weighted because of the adenoid cystic carcinomas, give some indication of the frequency and behavior of salivary-type carcinomas of the sinonasal tract. They are numerically dominated by pleomorphic adenomas and adenoid cystic carcinomas, have no known epidemiologic factors (unlike some surface adenocarcinomas), and often considerably differ histopathologically from their counterparts in major salivary glands.

The uncertainty over surface epithelial versus submucosal gland origin for the salivary-type neoplasms has led investigators to classify the malignant variants as only high-grade or low-grade on the basis of histologic appearance.[3,9] It is noteworthy that most of the salivary-type carcinomas have been low-grade. It is also noteworthy that some of

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From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

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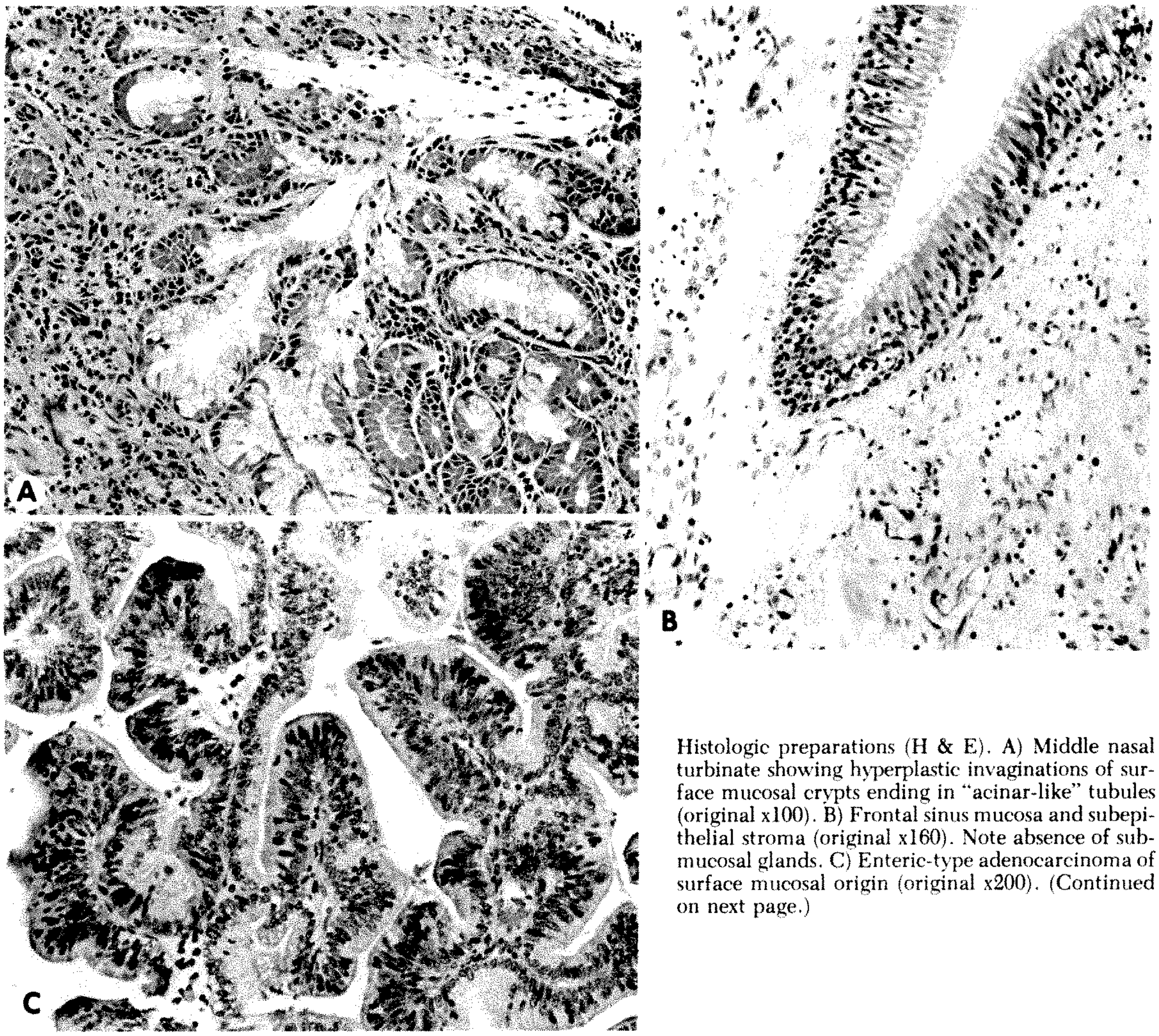


Histologic preparations (H & E). A) Middle nasal turbinate showing hyperplastic invaginations of surface mucosal crypts ending in "acinar-like" tubules (original x100). B) Frontal sinus mucosa and subepithelial stroma (original x160). Note absence of submucosal glands. C) Enteric-type adenocarcinoma of surface mucosal origin (original x200). (Continued on next page.)

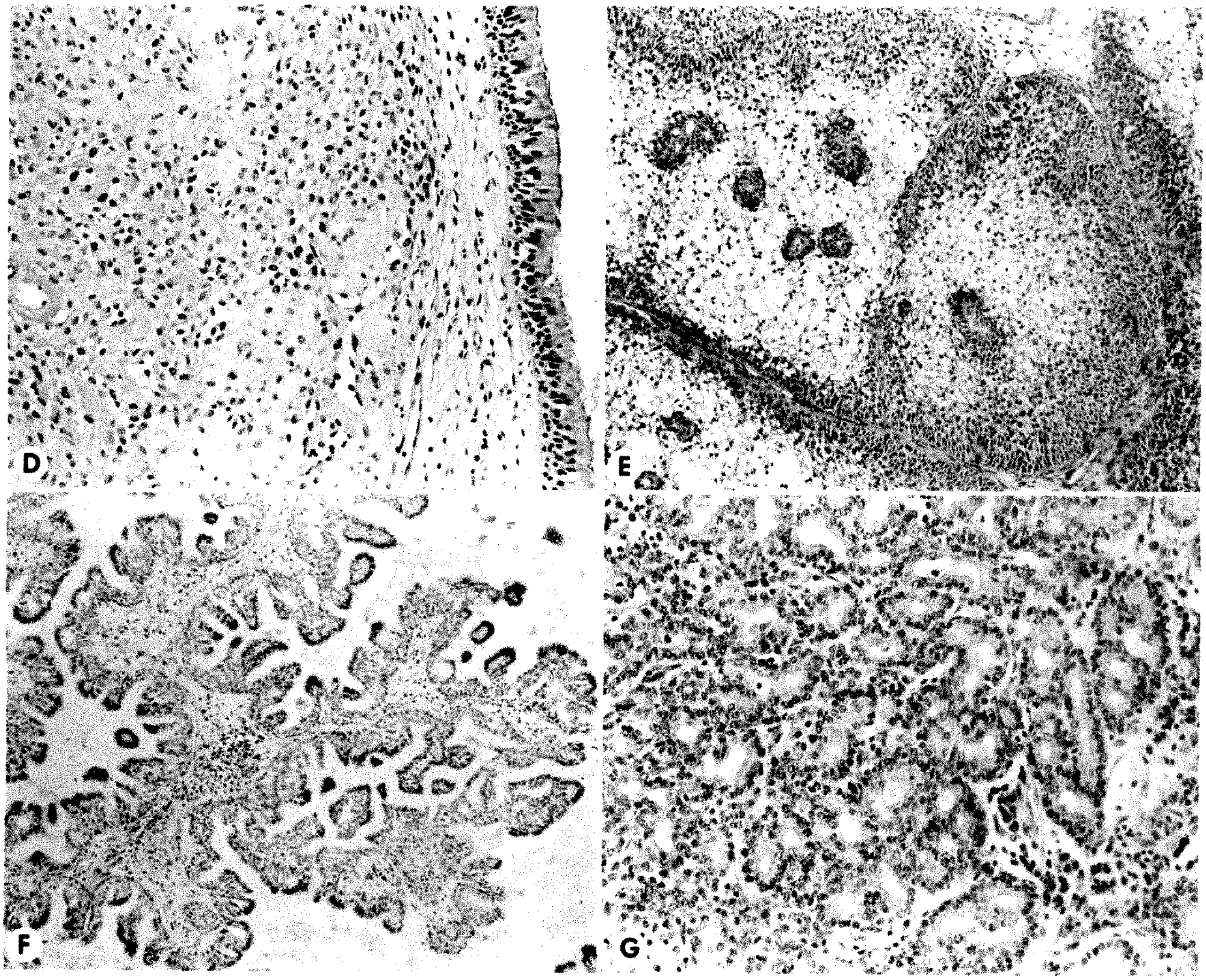
the same investigators[10] have had no difficulty in distinguishing surface adenocarcinomas from salivary-type carcinomas in the nasopharynx, in which there is an easily defined seromucous gland layer.

Histogenetically, all glandular neoplasms of the sinonasal tract take origin from stem or reserve cells that are resident in 1) the surface epithelium, 2) the seromucous derivatives of the invaginated surface epithelium, and 3) junctions between the two epithelia.

Benign glandular papillomas of the surface epithelium are rare. The adenocarcinomas are classified as low-grade or high-grade and resemble adenocarcinomas at any other mucosal site of the body, especially the gastrointestinal tract.[3,9,11] They may be papillary or sessile-infiltrative, may be poorly or well differentiated, and in their often striking similarity to enteric adenocarcinomas, can manifest Paneth's cells and produce cell-localized enteric hormones (see Figure, C). The surface adenocarcinomas also often have strong epidemiologic linkages.[12,13]

Pleomorphic adenomas in the sinonasal tract are almost exclusively intranasal, although secondary extensions into the paranasal sinuses may occur. In the nasal cavity the bony or cartilaginous nasal septum is the site of predilection. Twenty percent arise from the lateral nasal wall, usually from a turbinate.[14] In over 30 years, we have seen only two in the sinuses, both in the maxillary antrum. The adenomas manifest no sex predilection, present most often in the third to sixth decades of life, and usually show a greater cellularity (myoepithelial) than their major salivary gland counterparts (see Figure, D). They can range in size from less than 0.5 cm to over 7.0 cm and are most often polypoid and broad-based in configuration. The overlying mucosa may be attenuated but not ulcerated unless there has been trauma to the area. Recurrences of the pleomorphic adenomas are uncommon. Compagno and Wong[14] cite a 10% rate after first excision. Left alone, however, pleomorphic adenomas of the sinonasal tract can be locally destructive and extensive in their expansion.

Mononorphic adenomas of any type, including oncocytomas,[15] are rare in the nasal cavity and paranasal sinuses, but as it is with pleomorphic adenomas, they can assume a locally infiltrative behavior.



D) Pleomorphic adenoma of nasal septum (original x160). This microscopic field shows myoepithelial cells and focal chondroid change in tumor. E) Inverting (lateral wall) schneiderian papilloma with mucinous cell differentiation (original x60). This is one type of sinonasal lesion that has been misclassified as mucoepidermoid carcinoma. F) Salivary-type papillary adenocarcinoma of turbinates (original x60). Histologically, this carcinoma is low-grade. G) Low-grade salivary-type adenocarcinoma of nasal septum (original x200).

Mucoepidermoid[16] and acinic cell carcinomas[17] are among the least encountered salivary-type carcinomas in the sinonasal tract, and surgical pathologists should not expect either to show the "classic" major salivary gland phenotype. Adenosquamous carcinomas, surface squamous cell carcinomas with residual mucous glands, and schneiderian papillomas with mucous glands are the lesions most often misclassified as mucoepidermoid carcinomas (see Figure, E). Only eight acinic cell carcinomas have been reported: four from the nasal cavity and four from the paranasal sinuses, primarily from the maxillary antrum.[18]

The majority of salivary-type carcinomas of the nasal cavity and paranasal sinuses are biologically and histologically low-grade neoplasms with a well-developed glandular pattern, very uniform nuclei, and minimal mitotic activity.[9] Cells may be oncocytoid, amphophilic, or clear. They possess no capsule and it is difficult to discern a clear demarcation of tumor from adjacent seromucous glands. Often an adenoma or adenomatous hyperplasia is suggested by these highly differentiated neoplasms. A "back-to-back" crowding of the small glands without intervening stroma is a typical feature (see Figure, F). On occasion, a cystic pattern is displayed. Papillary infoldings are often present in various degrees (see Figure, G).

Kleinsasser[5] has applied the name "terminal tubulus adenocarcinoma of nasal seromucous glands" to this type of low-grade salivary-type lesion. Like Heffner et al,[9] Kleinsasser[5] indicates the neoplasms are primarily nasal (turbinate, middle concha) or ethmoidal in site of origin.

Despite a usually low-grade histopathologic appearance, salivary-type adenocarcinomas can display a morbid (recurrences) and even lethal behavior. Heffner et al[9] note a 30% recurrence rate but qualify the observations by indicating that the first

TABLE 1. HISTOLOGIC TYPES OF CARCINOMAS OF NASAL CAVITY AND PARANASAL SINUSES

Histologic Type of Carcinoma	*Nasal Cavity*	*Maxillary Sinuses*	*Other Sinuses*
Squamous cell carcinoma and "transitional cell" carcinoma	1,106	1,692	350
Undifferentiated carcinoma	186	321	141
Adenocarcinoma	171	193	132
Salivary gland–type carcinoma	30	75	28
Total	1,493	2,281	651

Data from Muir and Nectoux.[7]

TABLE 2. FIVE-YEAR SURVIVAL OF SINONASAL MALIGNANCY ACCORDING TO HISTOLOGIC CLASSIFICATION

Histologic Type of Neoplasms	*5-Year Survival (%)*
Mucosal melanoma	9.1
"Anaplastic" carcinoma	20.8
Squamous cell carcinoma	29.2
"Transitional cell" carcinoma	30.0
Lymphoma	34.6
Adenocarcinoma	38.2
Salivary-type carcinoma	63.6

Data from Robin et al.[8]

surgical removal is not always inclusive. Kleinsasser[5] and Heffner et al[9] also record instances of uncontrolled local disease with distant metastases. Prior to metastasis, the salivary adenocarcinomas became considerably less differentiated.

High-grade salivary-type adenocarcinomas do occur, eg, signet ring, colloid, and ductal carcinomas. Surface adenocarcinomas can also assume these phenotypes. Given their high grade and infiltrative qualities, a salivary versus surface origin is only academic.

Adenoid cystic carcinomas at any site appear to have an accelerated biologic course if a solid architecture is present in the carcinomas. This rule applies also to sinonasal adenoid cystic carcinomas.[3] For any grade of sinonasal adenoid cystic carcinoma, however, a number of factors are deterrents to a long-term prognostic outlook. Late detection; a complex, contiguous anatomy; difficulty in achieving negative surgical margins; and proximity of cranial nerves, organs of special sense, and the brain all hamper "cure" of this salivary carcinoma. A considerable number present with advanced (T3 and T4) cancers and as a consequence will almost always show invasion and destruction of adjacent normal tissue. According to Goepfert et al,[3] perineural, perivascular invasion, and extension into bone are seen as frequently in nonsolid as in solid adenoid cystic carcinomas of the nasal cavity and paranasal sinuses, but there is a significantly higher mortality with solid adenoid cystic carcinomas.

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FOR THE RECORD

At least three views exist about the cause of Spastic Dysphonia: physicians believe the cause is medical; psychiatrists believe it is psychological; and my position as a voice and speech pathologist is that Spastic Dysphonia is caused by misuse and abuse of the speaking voice. It is a mechanical problem, with psychological overtones. The individual is figuratively talking with the brakes on, squeezing the voice from the lower throat, and the breathing is in the wrong gear.

In 1980 in the Proceedings of the 18th Congress of the International Association of Logopedics and Phoniatrics, I reported on nine patients who had recovered from Spastic Dysphonia by Direct Voice Rehabilitation and five patients who were recovering. One patient, Dr. Don Dodson, who discussed his voice problem at this meeting, fully recovered his voice the next year. But Herbert Dedo, M.D., in the April 1991 issue of the Annals of Otology, Rhinology & Laryngology, writes: "Regarding need, many otolaryngologists, voice therapists, neurologists, and psychiatrists, after correctly diagnosing a case of SD, still are unaware that it is not curable (ie, spasticity is not eliminated) with voice therapy . . ." (pg. 277).

In 1982, at Cedars-Sinai Medical Hospital, Los Angeles, I presented three patients who had confirmed severe Spastic Dysphonia to an audience of Ear, Nose, and Throat doctors. These patients told the audience how they had recovered their speaking voices by Direct Voice Rehabilitation. But Herbert Dedo, M.D., in the above mentioned journal writes: "The only effective treatment at the present time is paralysis of one vocal cord temporarily with botulin injection or permanently with left RLN section . . . " (pg. 278).

In 1990, I was again invited to return as guest speaker at Cedars-Sinai Medical Center. This time I presented five patients with diagnosed Spastic Dysphonia and discussed how I had helped them with Direct Voice Rehabilitation. Regarding the treatment of Spastic Dysphonia by Direct Voice Rehabilitation in patients seen in his private practice group, a very prominent otolaryngologist, Edward A. Kantor, M.D., Chairman, Division of Otolaryngology, Head and Neck Surgery, Cedars-Sinai Medical Center, Los Angeles, has this to say: "Dr. Morton Cooper has shown unusual expertise in treating patients with Spastic Dysphonia. His methods of voice therapy in our patients afflicted with this markedly disabling disease have been highly successful."

Over the past fifteen years, I have been to meetings of the American Speech-Language-Hearing Association, the California Speech-Language-Hearing Association, and the International Association of Logopedics and Phoniatrics, presenting with tapes or with actual patients the recovery from Spastic Dysphonia by Direct Voice Rehabilitation. In articles and videos (in local TV shows on American Cable and Century Cable. I have reported on 'before' and 'after' patients who have had Spastic Dysphonia.

The late Henry Fonda had Spas
Through a program of Direct Voice
Fonda was able to recover his voic
Golden Pond," a movie for which h
Oscar. Another patient, Dr. Don Do
Angeles Times interview that he ha
from Spastic Dysphonia. Zelda Poll
Spastic Dysphonia while teaching,
tell about her recovery.

People come from all over the w
resolving Spastic Dysphonia. A pro
the Middle East, having been direct
doctor in the United States, on an F
on a golf ball." By Direct Voice Reh
patient recovered in a year. I have
reports from him; he has retained a
the past fifteen years. Jim Johnson
Mid-West, having had severe Spas
almost nine years and trying all kin
unsuccessfully (even going to the M
talking with a normal voice; he und
daily one month program of Direct
with me. He says his voice recover
voice remains excellent after five ye

I have found that Spastic Dysph
the monster voice, isn't hopeless ar
excellent prognosis in my office. My
from those of my colleagues, and I
of what some of my colleagues and
do for Spastic Dysphonia. Patients
Dysphonia are usually not given op
botulin injection. The downside of th
find, is not presented to these patie
Rehabilitation is a holistic, conserva
invasive and natural way of helping
Dysphonia and patients should be g
alternative approach. Are the medic
speech pathology associations play
voice?

In 1973 in my textbook, Modern
Vocal Rehabilitation, I wrote about r
Spastic Dysphonia. In my two most
Change Your Voice, Change Your L
With Your Voice, I discuss the way
more effective voice, and I detail ho
from Spastic Dysphonia have been
Direct Voice Rehabilitation program

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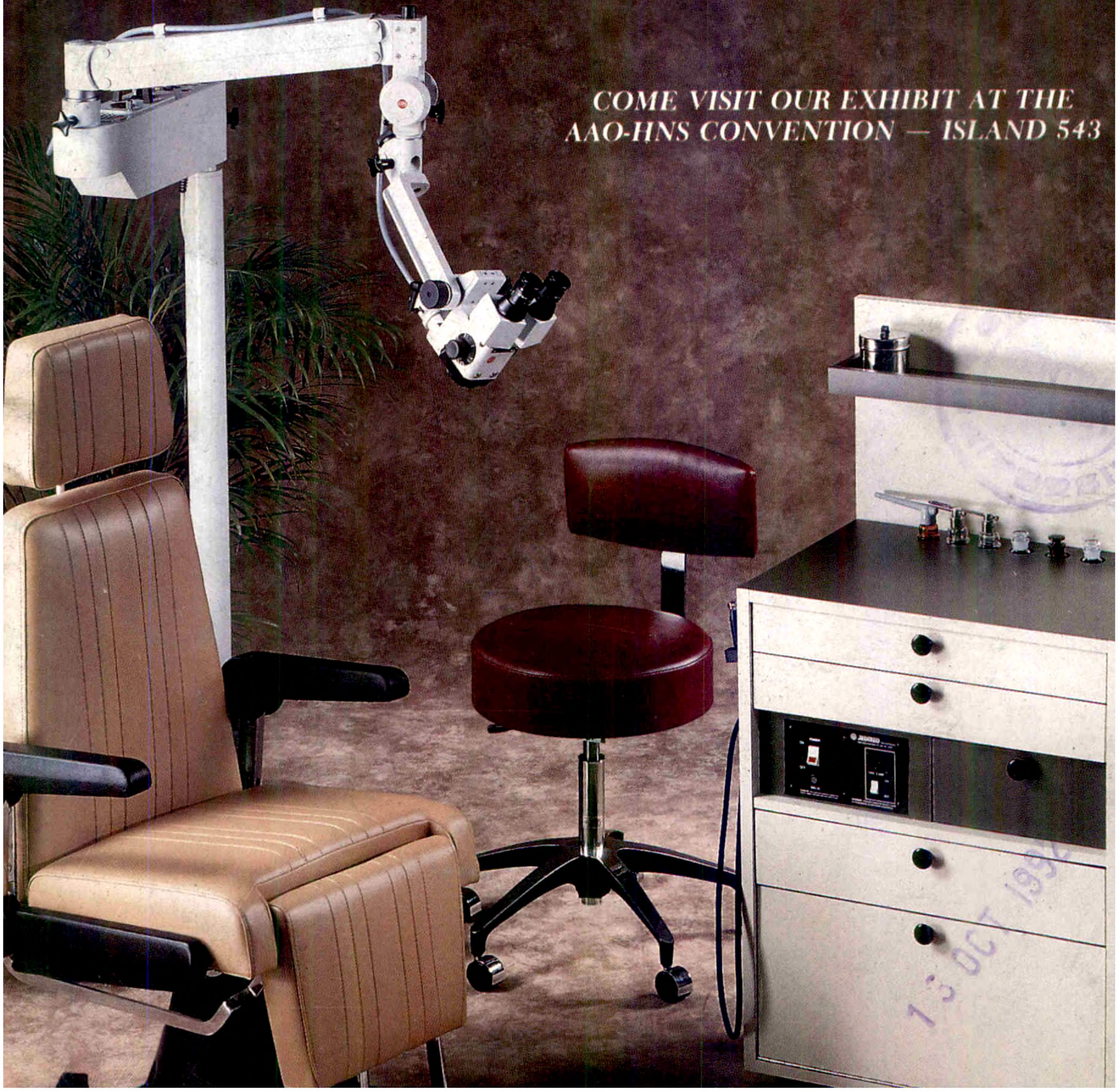

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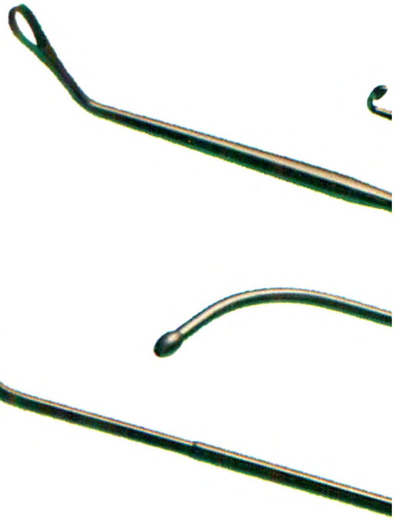

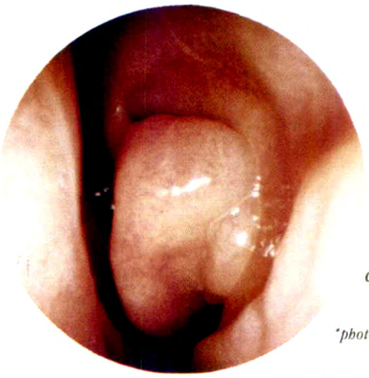

*Concha bullosa on left side bulging into lateral nasal wall. Entrance to middle meatus blocked and a polyp is arising from the contact area.**

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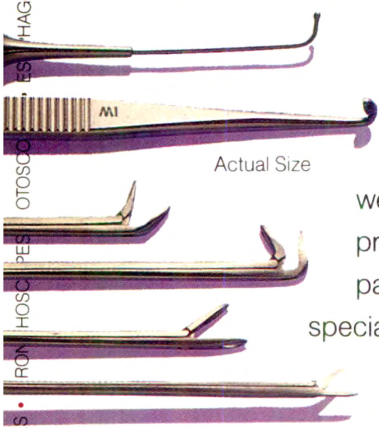

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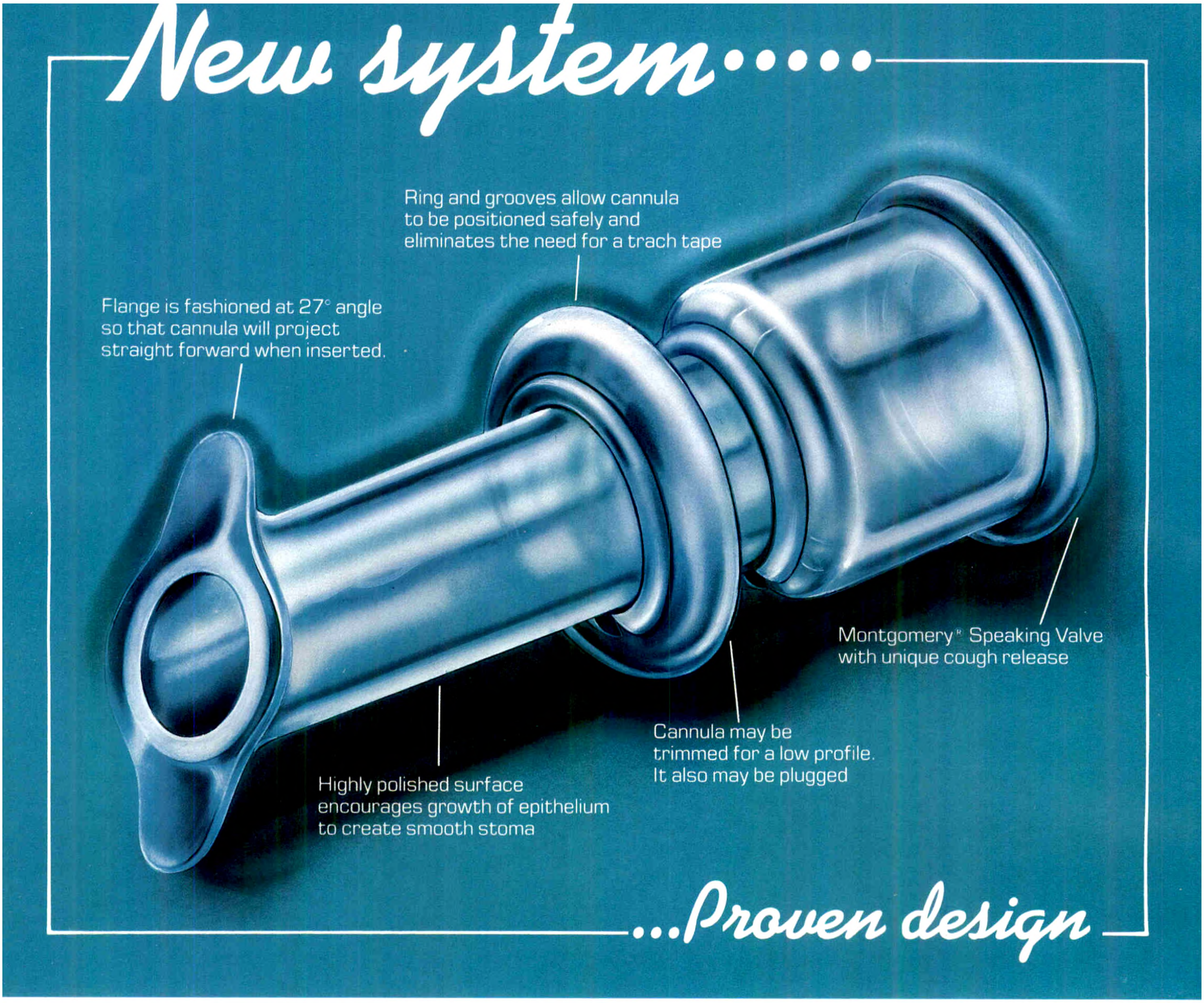
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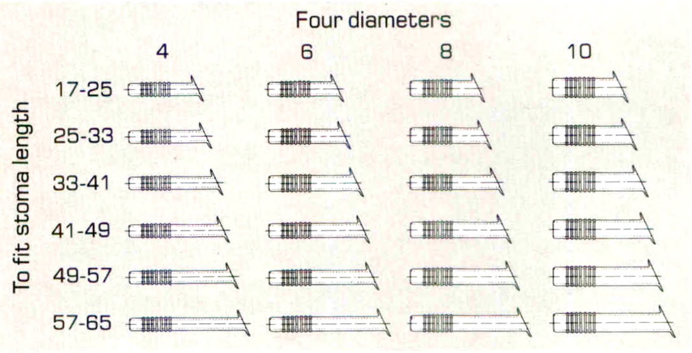
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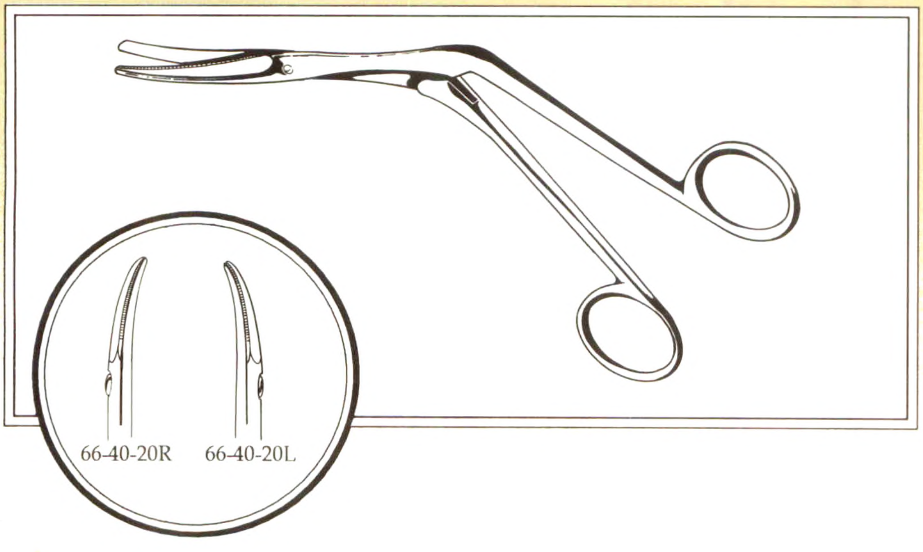

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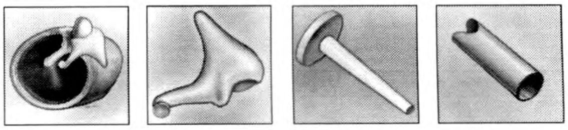

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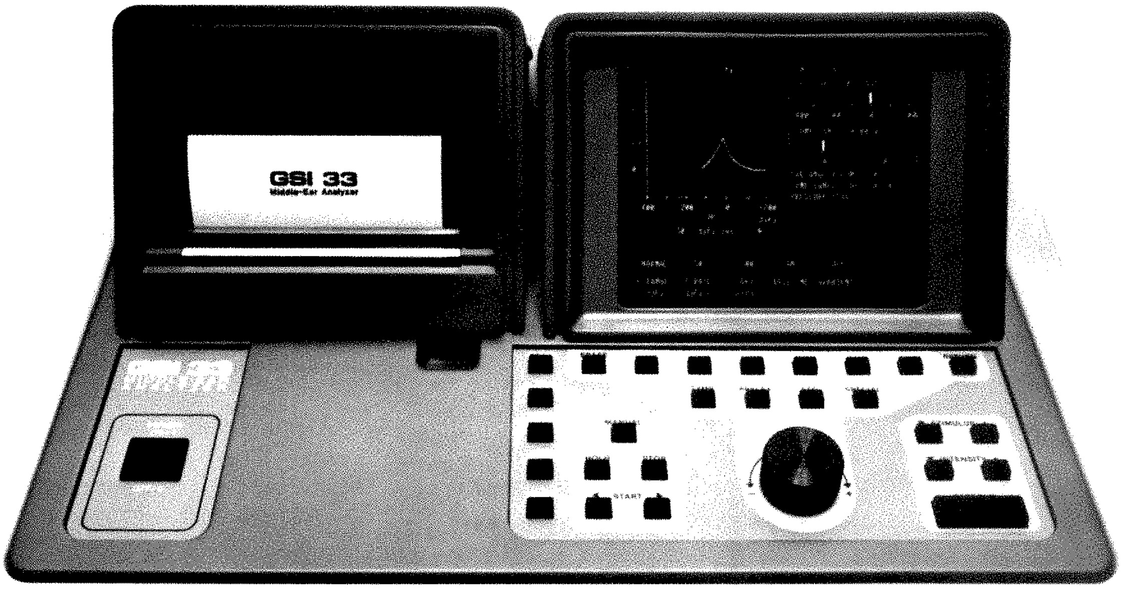

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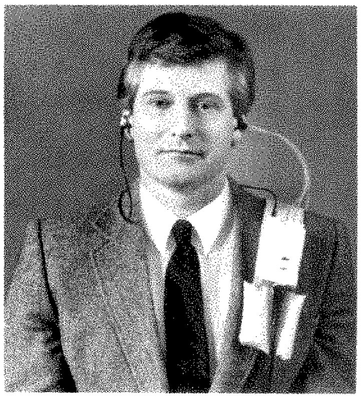

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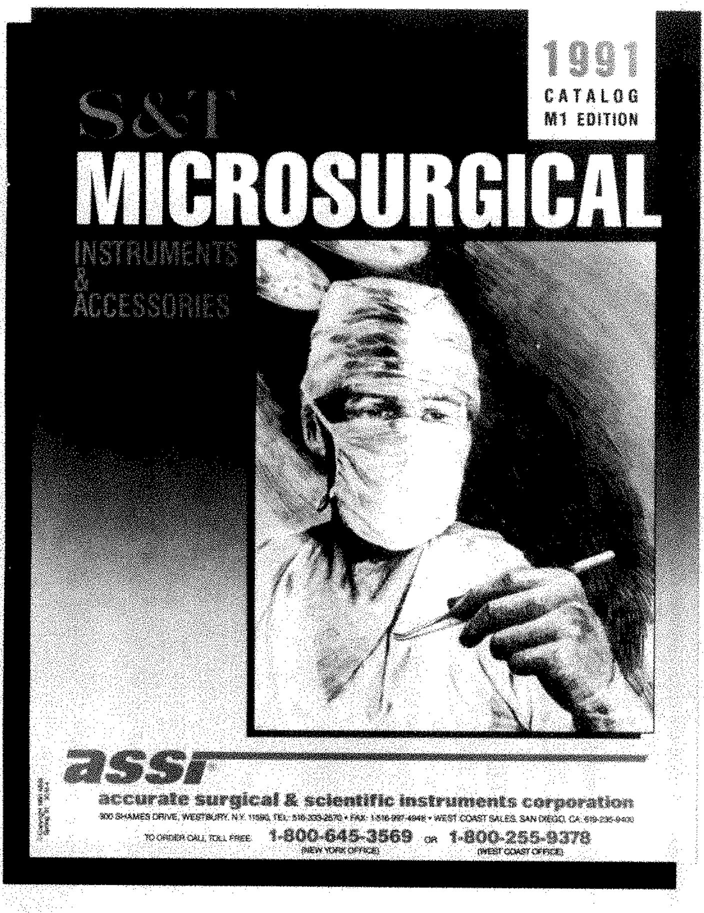

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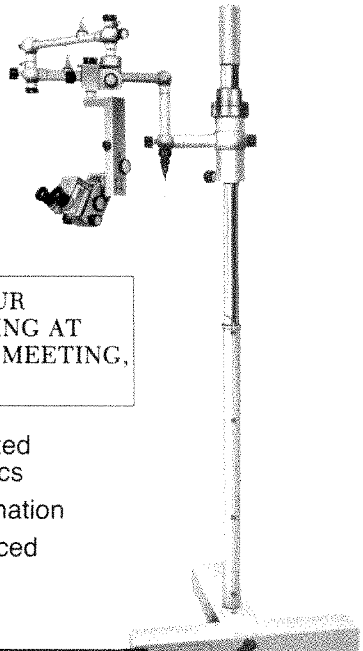

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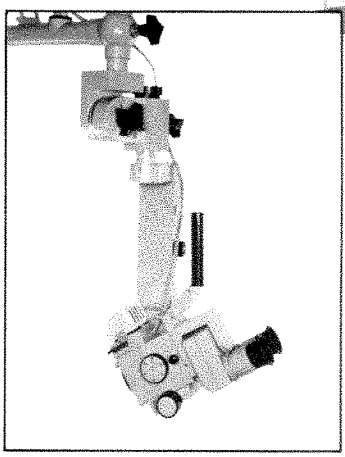

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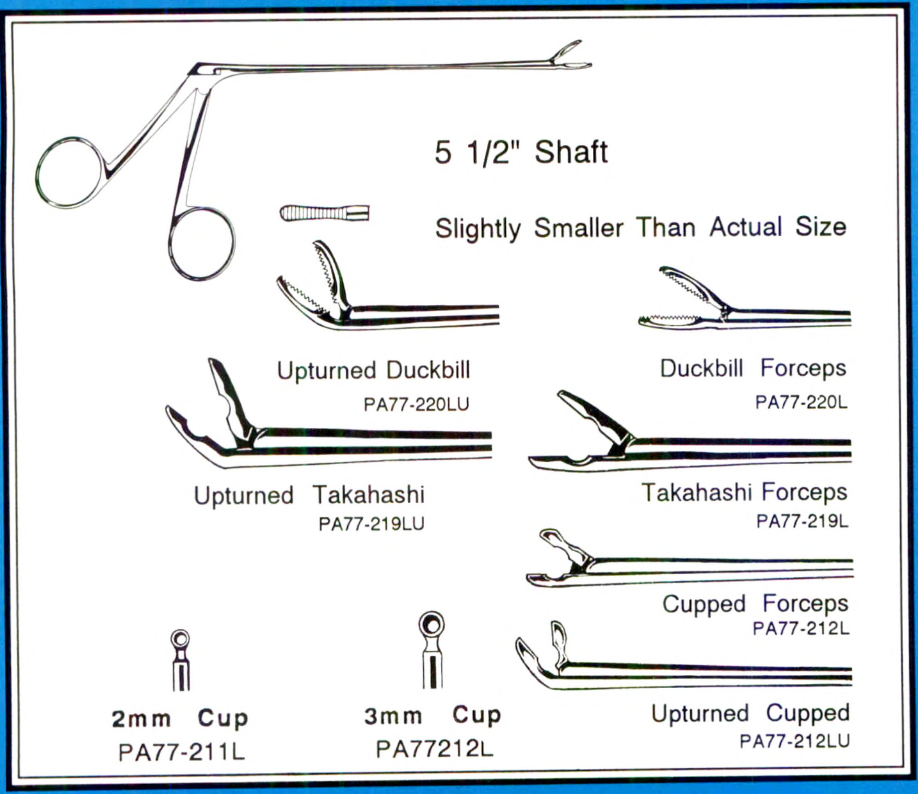
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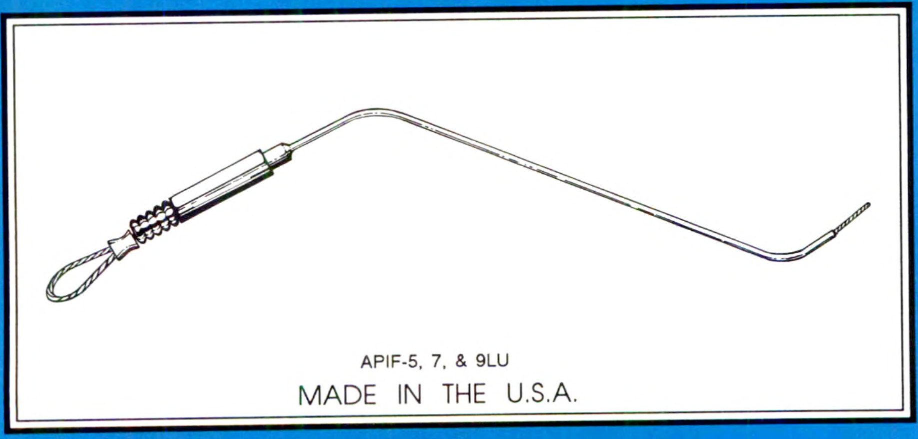
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ELECTRODE INSERTION TRAUMA IN COCHLEAR IMPLANTATION

CDR Michael J. O'Leary, MC, USN
San Diego, California
William F. House, MD
Newport Beach, California
Jose Fayad, MD
Los Angeles, California
Fred H. Linthicum, Jr, MD
Los Angeles, California

Residual hearing conservation may be important in cochlear implantation of children and of adults with disabling tinnitus responsive to extracochlear stimulation. Damage to the neural elements of the cochlea during electrode insertion may have a negative impact on residual hearing conservation. Histologic analysis of eight temporal bones with cochlear implants reveals trauma at essentially two locations: the round window insertion site and along the basal turn of the cochlea. In four of the bones, insertion at the round window resulted in damage to the osseous spiral lamina and the electrode was inserted through the scala media into the scala vestibuli. Evidence of secondary reactive osseous formation was also noted in these bones. This paper relates the surgical anatomy of the round window to histologic findings and microanatomical dissections. Recommendations for implantation surgery include creation of a cochleostomy by removal of the floor of the round window niche and a superior-to-inferior angle of electrode insertion.

KEY WORDS — cochlear implant, round window, surgical trauma.

INTRODUCTION

A clear safety record for cochlear implantation has been established during the past decade. Early concerns regarding the effects of electrode insertion trauma and stimulation of the vestibular labyrinth or the central nervous system have been satisfied. With the investigation of implants for patients with residual hearing, the issue of electrode trauma may once again be significant.

L. M. Dye et al (unpublished observations, 1987) noted no change in postoperative residual hearing in 8 of 20 patients (40%) implanted with the House 3M implant. Eight other patients suffered bilateral deterioration of residual hearing, which was felt to be secondary to the underlying disease process, as the contralateral side had not been implanted. In the remaining 4 patients, loss of residual hearing on the implanted side only was attributed to the surgical trauma. Rizer et al,[1] measuring residual hearing in 7 implant patients (6 with the 22-channel device and 1 with the House 3M single-channel), found an average 25-dB deterioration in residual hearing across the speech frequencies. Bogess et al[2] reported a similar "significant downward shift in the hearing thresholds of the implanted ear" in 20 patients with the Nucleus 22-mm electrode array.

As electrode insertion trauma to the membranous cochlea may be the principal mechanism for residual hearing loss, we assessed the damage at the round window insertion site in temporal bones with cochlear implants.

MATERIALS AND METHODS

The House Ear Institute temporal bone collection contains 17 bones from 13 patients. On microscopic review, 8 bones from 6 patients contained adequate preservation of round window and basal turn structures to assess electrode insertion trauma. The Table lists the causes of deafness and types of implant in these 8 ears.

All temporal bones were fixed in formalin, decalcified in ethylenediaminetetraacetic acid, and embedded in celloidin. Specimens were sectioned 20 μm thick in the horizontal plane and every 10th section was stained with hematoxylin and eosin and mounted on a glass slide. Damage caused by electrode insertion was assessed by means of light microscopy. All the specimens are presented from below with the lateral border superior.

RESULTS

Drilling was felt to be minimally traumatic to the osseous spiral lamina and scala media in four speci-

CLINICAL AND HISTOLOGIC DATA ON EIGHT TEMPORAL BONES WITH COCHLEAR IMPLANTS

Bone No.	*Age of Patient*	*Cause of Deafness*	*Implant Type*	*Electrode Length (mm)*
Minimal trauma				
1*	58	Ototoxic	House	16
2	55	Acquired	House 3M	6
3	67	Otosclerosis	House 3M	6
4*	61	Acquired	House	16
Trauma				
5	71	Unknown†	House 3M	6
6*	61	Acquired	Nucleus	22
7*	58	Ototoxic	House	16
8	47	Otosclerosis	Prototype	10-20

*Implanted bilaterally.

†Amorphous neural degeneration by histologic examination.

From the House Ear Institute, Los Angeles, California (O'Leary, Fayad, Linthicum). The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

Presented at the Second International Cochlear Implant Symposium, Iowa City, Iowa, June 4-8, 1990.

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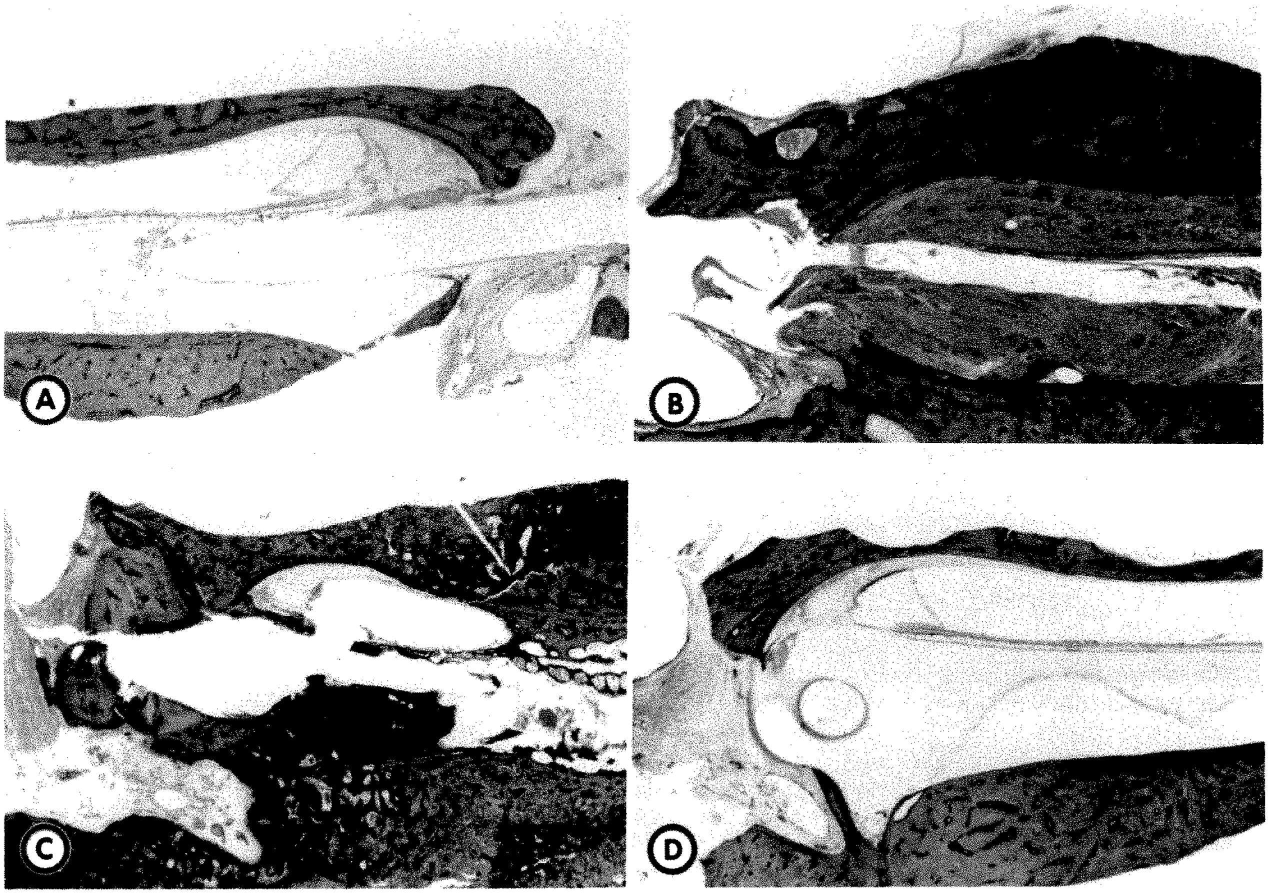

Fig 1. Bones with minimal insertion site trauma. A) Right scala tympani electrode track just inferior to osseous spiral lamina. B) Left cochlear neuroma. C) Left diffuse otosclerosis with scala tympani electrode path. D) Left electrode path with intact scala media.

mens. In one bone a short electrode inserted through the round window passed successfully into the scala tympani just inferior to the osseous spiral lamina (Fig 1A). Despite a vigorous fibrotic reaction, there was little evidence of osteogenic reaction. In another bone, the track of a short electrode remained entirely within the scala tympani (Fig 1B). A large intracochlear neuroma noted in this bone partially obstructed both the scala tympani and the scala media. The tumor likely was the cause of this patient's slowly progressive hearing loss in an only hearing ear. Surgical records noted that insertion was without difficulty.

In the third bone, diffuse otosclerosis partially obstructed the scala vestibuli, although the electrode path remained within the scala tympani without disruption of the osseous spiral lamina (Fig 1C). In the fourth bone, without trauma despite a rather lateral entry site, the long electrode track remained within the scala tympani and only minimally disrupted the spiral ligament (Fig 1D). The scala media and basilar membrane remained intact in the region of the round window, although considerable trauma was noted more distal along the basal turn.

The remaining four specimens exhibited a considerable degree of trauma, and none of the electrodes remained within the scala tympani. In one bone, a "high" insertion placed the 6-mm electrode entirely within the scala vestibuli. There is partial damage to the osseous spiral lamina with complete disruption of the scala media in the region of the round window (Fig 2A). A severe bilateral loss of dendrites and supporting cells was likely caused by the underlying pathologic process. Osteoblastic reaction was mild. A second bone, with a long, single-channel electrode, had disruption of the spiral ligament and focal osteoid formation (Fig 2B). The third bone had a more pronounced osteogenic reaction obliterating the scala tympani. The electrode path was entirely within the scala vestibuli (Fig 2C). A similar diffuse osteogenic reaction occurred in the last bone with a prototype device requiring insertion of four separate electrodes through the round window niche (Fig 2D). Despite the prominent otosclerosis, extensive metaplastic bone formation is also present. Several electrode tracks were distinguished within the diffuse fibrotic reaction.

DISCUSSION

Fifty percent of the implanted specimens in this study revealed considerable trauma to the osseous

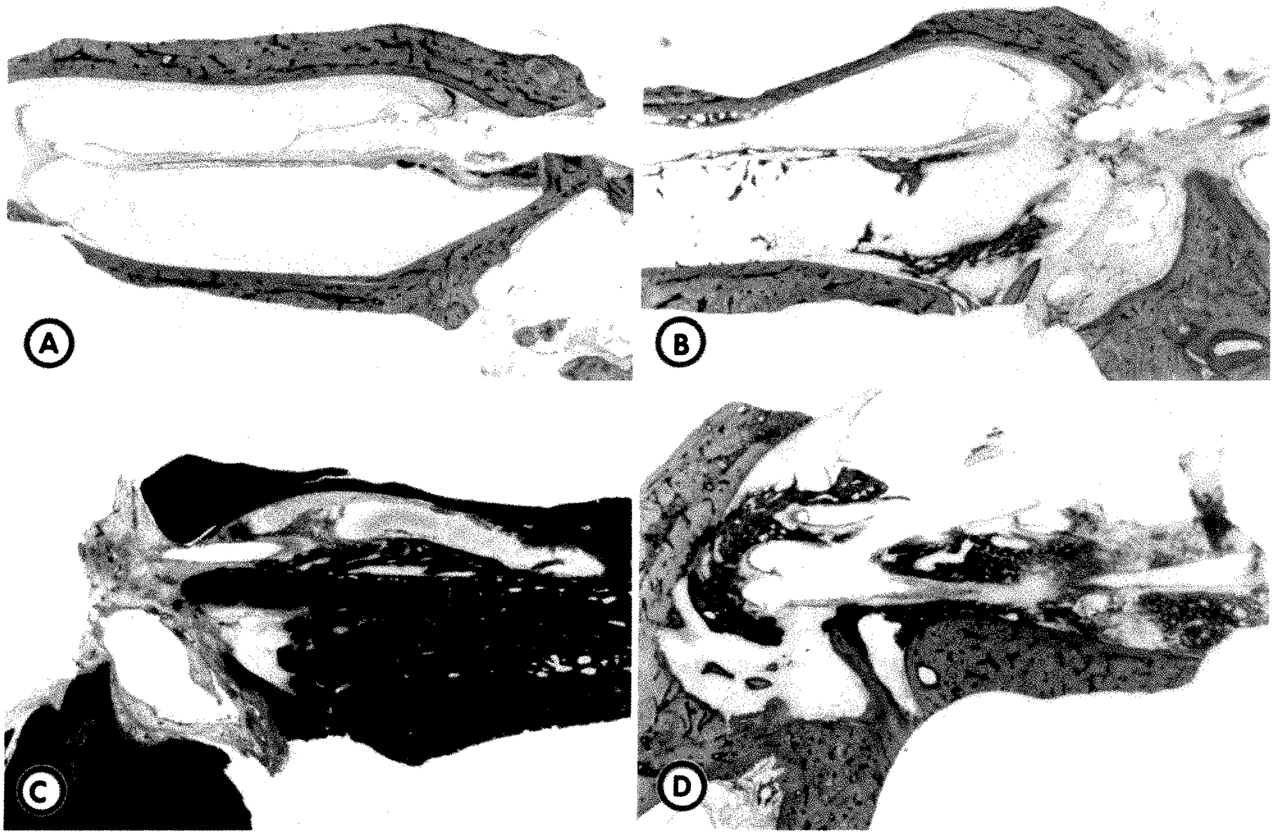

Fig 2. Bones with traumatic electrode insertions. A) Right electrode path directly into scala vestibuli with disruption of osseous spiral lamina and basilar membrane. B) Right electrode track directed at osseous spiral lamina. Note foci of osteoid formation. C) Left scala vestibuli insertion site with osteogenic obliteration of scala tympani. D) Left diffuse otosclerosis with reactive bone formation and multiple electrode tracks.

spiral lamina and membranous cochlea at the round window insertion site. The preponderance of osteogenic reaction in the traumatized cases contrasts markedly with those cases in which the electrode path remained entirely within the scala tympani. These findings are consistent with earlier findings in cats of extensive osteoneogenesis associated with fractures of the osseous spiral lamina and disruption of the endosteum.[3,4] Damage to radial nerve fibers in these cats was associated with a retrograde de-

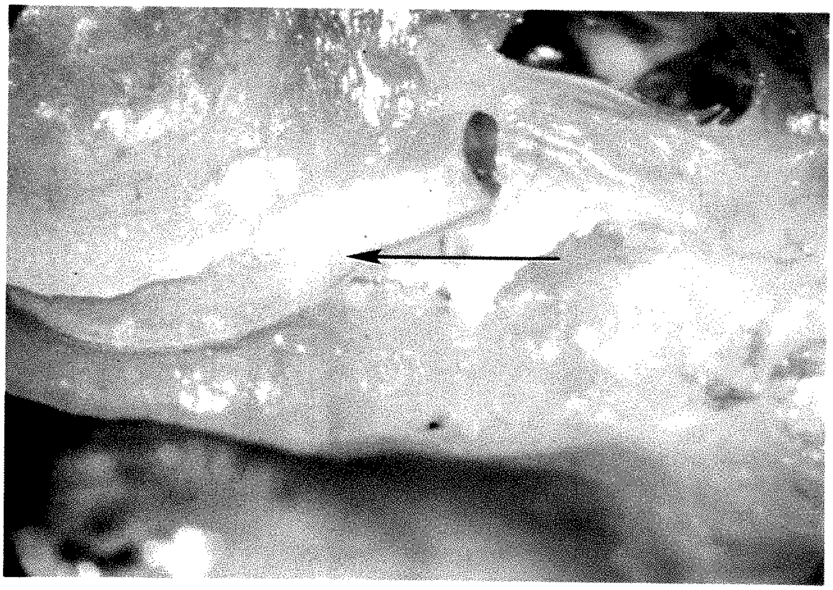

Fig 3. Inferior view, left round window and cochlear basal turn. Lateral walls of niche and promontory have been removed. Arrow shows potential electrode track passing from scala tympani through osseous spiral lamina and resting in scala vestibuli. Note almost parallel relationship of spiral lamina to plane of round window.

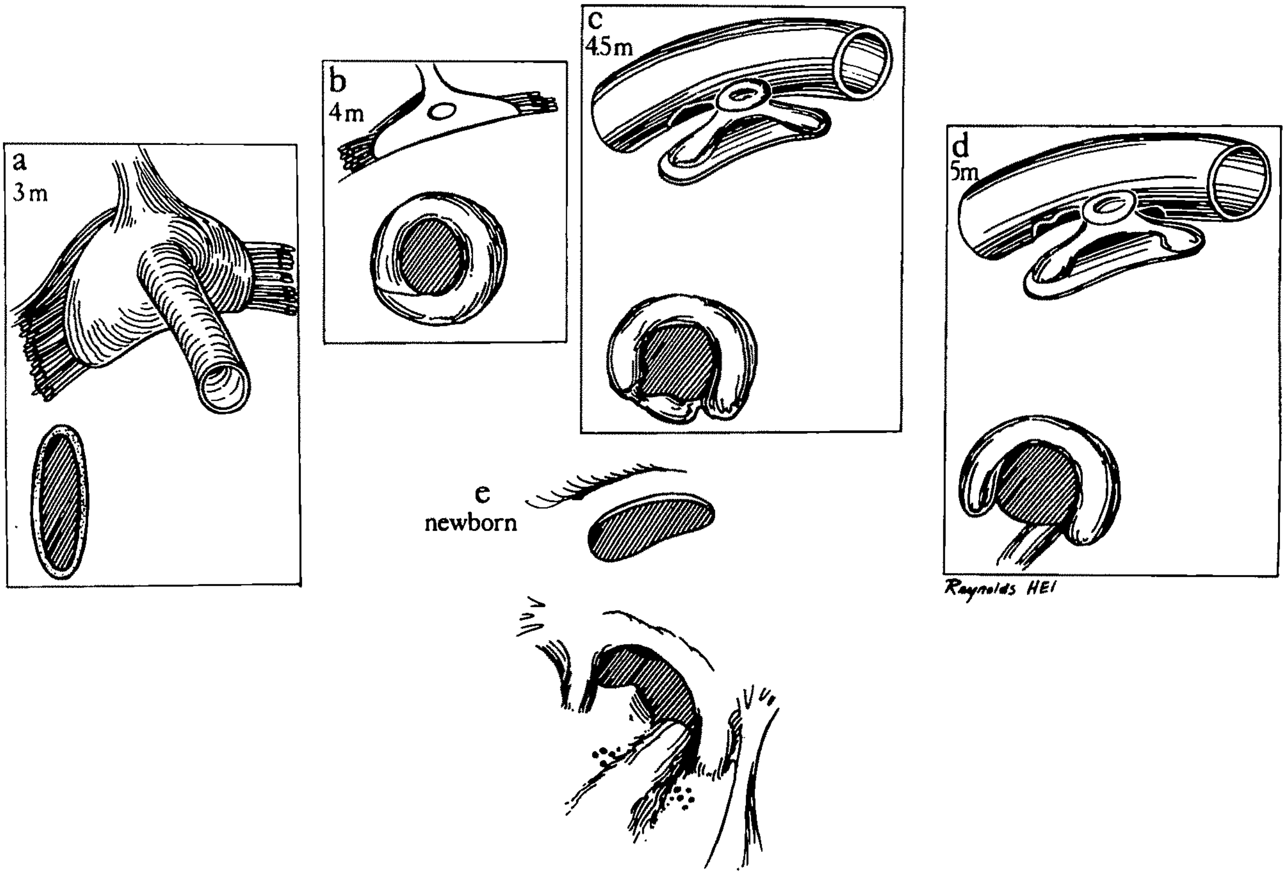

Fig 4. Diagram of embryologic stages (a-e) of oval and round window development. Note ultimate contribution of cordlike *fustis* to floor of round window niche. (Adapted with permission.[6])

generation and spiral ganglion cell loss, although this was not the case in human implanted temporal bones reported recently.[5]

The round window niche provides direct intracochlear access for electrode implantation. The anatomical features of this region, however, place the membranous cochlea and osseous spiral lamina at considerable risk when an electrode is inserted directly through the round window membrane (Fig 3). Proctor[6] noted the contribution of the *fustis* to the embryologic development of the floor of the round window niche, obscuring much of the scala tympani chamber (Fig 4[6]). Insertion of an electrode perpendicular through the round window membrane virtually assures contact with the osseous spiral lamina and ultimate residency of the electrode in the scala vestibuli (Fig 5A).

Performance of a cochleostomy by removal of the floor of the niche affords a direct view to the scala tympani with little insertion trauma (Fig 5B). A su-

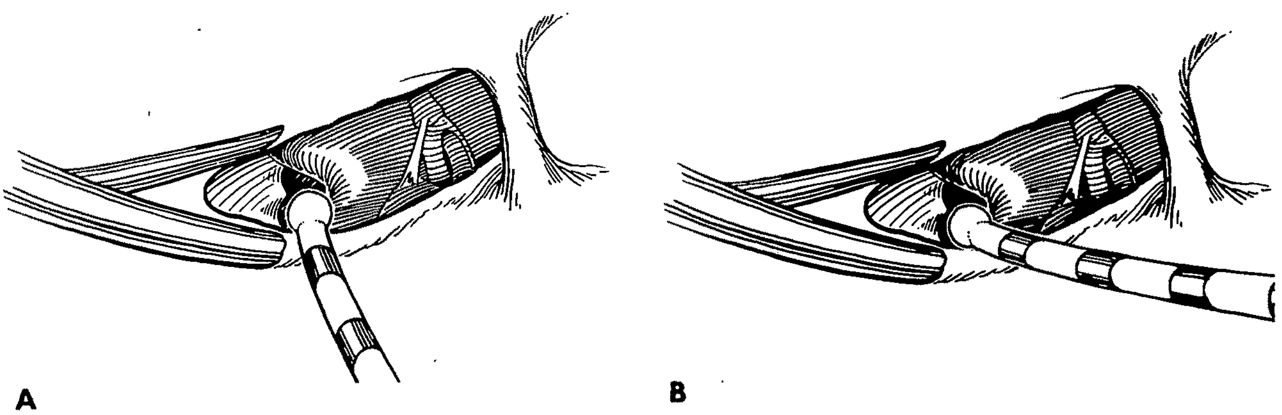

Fig 5. Diagrammatic representation of electrode insertions. A) Perpendicular insertion virtually assures trauma to osseous spiral lamina beneath. B) Superior-inferior insertion angle with cochleostomy in floor of round window niche helps preclude migration from scala tympani.

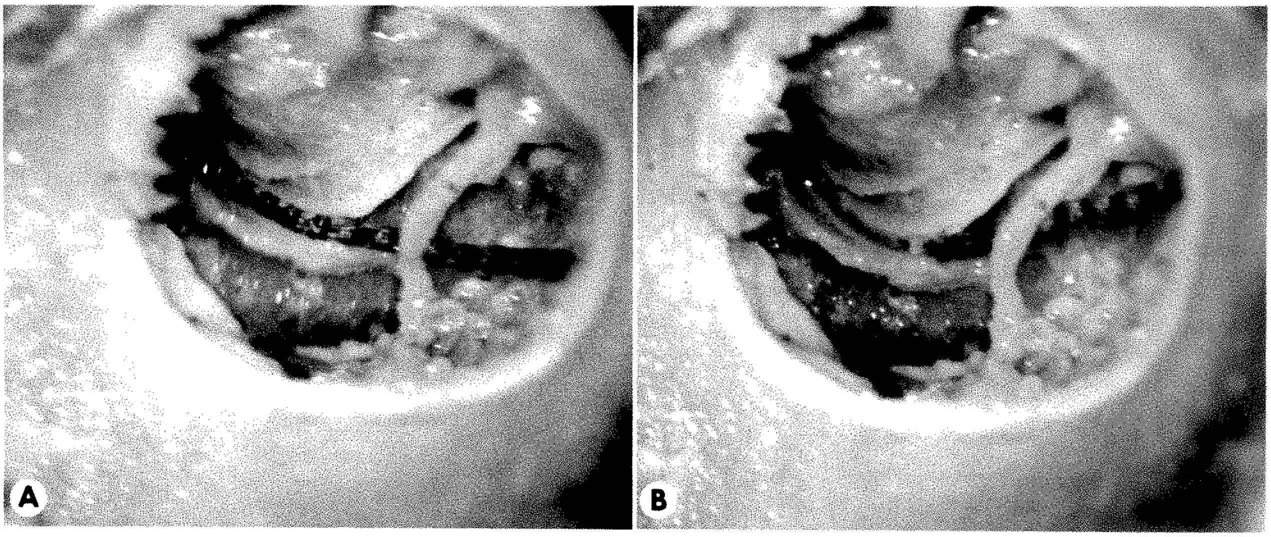

Fig 6. Views of skeletonized left promontory. A) Perpendicular transit of long electrode from scala tympani to scala vestibuli across osseous spiral lamina. B) Superior-inferior–directed electrode remains within scala tympani.

perior-to-inferior insertion angle, as advocated by Goycoolea et al,[7] without additional surgical approach helps minimize damage to the osseous spiral lamina and scala media. Regardless of approach, maintaining an electrode position in the scala tympani appears to reduce the incidence of insertion site trauma (Fig 6). Whether this translates into improved implant performance has yet to be determined.

CONCLUSION

Four of eight implanted temporal bones showed evidence of insertion trauma at the round window. According to these findings we suggest cochleostomy with removal of the floor of the round window niche, combined with a superior-to-inferior insertion angle, to best maintain initial electrode placement within the scala tympani.

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EFFECTIVENESS OF AN INTENSIVE SPEECH PERCEPTION TRAINING PROGRAM FOR ADULT COCHLEAR IMPLANT RECIPIENTS

JEAN-PIERRE GAGNÉ, PHD
LORNE S. PARNES, MD, FRCSC
MARGARET LAROCQUE, MCLSC
RAJAA HASSAN, MCLSC
SILVIA VIDAS, BSC
LONDON, CANADA

A staggered multiple baseline single-subject experimental design was used to assess the effectiveness of a postimplant intensive aural rehabilitation program. Four adults with an acquired profound hearing loss were provided with a Nucleus 22-channel cochlear implant. The subjects completed a speech perception test protocol once before their cochlear implant operation and at 3-month intervals for a period of 12 months postimplantation. Each subject participated in a 12-week postimplant intensive aural rehabilitation program. A comparison of the prerehabilitation and postrehabilitation results failed to reveal any systematic improvements in performance on the speech perception tests that could be attributed unequivocally to the aural rehabilitation program.

KEY WORDS — aural rehabilitation, cochlear implant, single-subject experimental design.

Most cochlear implant programs provide postoperative aural rehabilitation services.[1-7] Several studies have reported improvements in speech perception abilities following cochlear implantation.[1-5,7-13] It is recognized that several factors may contribute to the improvements in the performance of cochlear implant recipients, including 1) the additional sensory input provided by the cochlear implant device,[14] 2) the recipient's motivation to improve speech perception performance,[9,11] and 3) the effectiveness of the postimplant aural rehabilitation program that accompanies most cochlear implant programs.[4,6,7,13] The purpose of the present study was to evaluate the effectiveness of a postimplant speech perception training program on the improvements in speech perception skills observed among adult cochlear implant recipients.

Two investigations suggested that postimplant speech perception training programs may not provide significant benefits to adult cochlear implant recipients. In one investigation the improvements in speech perception displayed by six adult cochlear implant recipients were monitored for a period of 6 months postimplantation. A battery of speech perception tests was administered at 1-month intervals preimplantation and postimplantation. The investigation revealed that the largest gains in speech perception were observed during a period of 1 month postimplantation, that is, before the subjects participated in any speech perception training program.[14] Another study reported no significant long-term changes in speech perception skills for 15 subjects who participated in an aural rehabilitation program for more than 1 year postimplantation. The results of the investigation revealed no improvements in speech perception beyond those observed during the first 3 months postimplantation.[15] The authors concluded that the 3-month postimplant performance may predict long-term performance for cochlear implant recipients. However, in both of those studies it is not possible to rule out the possibility that postimplant intensive aural rehabilitation services improved speech perception skills, since all the subjects participated in an aural rehabilitation program soon after they received a cochlear implant. Finally, there are reports that the speech perception abilities of some individuals who did not participate in any systematic postimplant aural rehabilitation program were comparable to the performances of individuals who completed an intensive aural rehabilitation program[13] (also personal communication, 1988, M. Baker, Cochlear Nucleus Corp).

A recent investigation evaluated the benefits of an aural rehabilitation program for adult cochlear implant recipients.[7] An intensive (40 hours over a period of 10 days) aural rehabilitation program was provided to two groups of subjects. One group (five subjects) completed the training program 1 month after their hookup to the cochlear implant device, while the other group (nine subjects) completed the training program 9 months after their initial hook-

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From the Hearing Health Care Research Unit (Gagné), the Department of Communicative Disorders (Gagné, Parnes), and the Department of Otolaryngology (Gagné, Parnes), The University of Western Ontario, and the Department of Audiology and Vestibular Function, University Hospital (Parnes, LaRocque, Hassan, Vidas), London, Canada. This work was supported by research grants from the Department of Otolaryngology, The University of Western Ontario, London, Canada, and the University-Hospital Pooled Research Trust Fund, London, Canada. In addition, part of the research project (1989-1990) was funded by the Hearing Health Care Research Unit in the form of a Health System Linked Research Unit grant (Ontario Ministry of Health) held by J.-P.G.

Modified versions of this report were presented at the meeting of the Canadian Association of Speech-Language Pathologists and Audiologists, Vancouver, Canada, May 10-13, 1990; the Second International Cochlear Implant Symposium, Iowa City, Iowa, June 4-8, 1990; and the meeting of the Canadian Society of Otolaryngology; Head and Neck Surgery, Montreal, Canada, June 25-27, 1990.

up. On the basis of the results obtained for each group of subjects, the authors concluded that early training plus experience with the cochlear implant for a period of 9 months resulted in more improvements than experience alone on tests of audio-only and audiovisual consonant recognition, audio-only spondee recognition, and an audio-only primary stress test. Moreover, the authors reported that the subjects displayed additional post-aural rehabilitation improvements on the various speech tests even when the training program was postponed for 9 months after the initial hookup.

In the present study a staggered multiple baseline repeated single-subject experimental design was used to investigate whether an intensive postimplant speech perception training program designed specifically for Cochlear Nucleus multichannel cochlear implant recipients could account for postimplant improvements in speech perception abilities. The present report constitutes an interim report based on the partial findings obtained from four individuals.[1]

METHOD

Subjects. Subjects were four adults with a profound sensorineural hearing loss acquired after the development of speech and language. Each received a Nucleus Mini 22-channel cochlear implant (Cochlear Corp). In all cases, the 22 electrodes were inserted into the cochlea of the recipient at the time of the operation.

Subject KF was a woman 27 years of age on the date of her operation (April 11, 1988). At 17 years of age KF suffered from a sudden profound hearing loss due to meningitis. All the data reported for this subject were obtained while she wore a wearable speech processor with 17 active electrodes programmed in a bipolar stimulation mode. (Electrodes 1 through 4 were not activated.)

Subject AR was a woman 64 years of age on the date of her operation (August 29, 1988). Deterioration of her hearing sensitivity was first observed in the 1950s. The subject had a profound hearing loss for more than 12 years prior to her operation. All the data reported for AR were obtained while she wore a wearable speech processor programmed in a bipolar plus one stimulation mode.

Subject RO was a man 36 years of age on the date of his operation (March 20, 1989). The subject suffered from a progressive sensorineural hearing loss of unknown cause. Deterioration of his hearing sensitivity was first observed when RO was approximately 10 years of age. He had a profound bilateral hearing loss for more than 13 years prior to his operation. Initially, RO wore a wearable speech processor programmed in a bipolar mode. However, 283 days postoperatively he was fitted with a mini speech processor programmed in a bipolar stimulation mode.

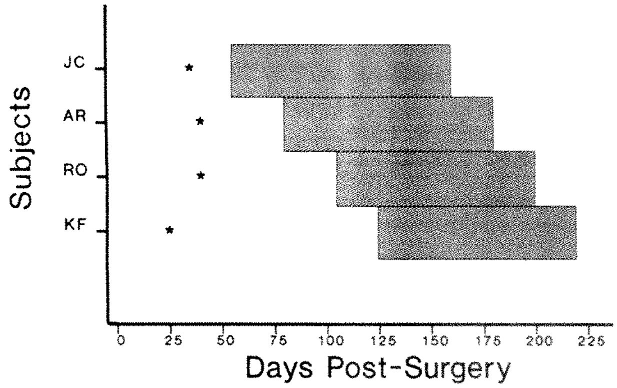

Fig 1. Schematic representation of experimental design used in present investigation. Individual subjects are identified on ordinate. Asterisk — day of initial hookup with speech processor, shaded rectangle — period of time during which each subject participated in intensive aural rehabilitation program.

Subject JC was a man 32 years of age on the date of his operation (October 24, 1989). At 12 years of age JC suffered from a progressive sensorineural hearing loss due to ototoxicity. He had a profound bilateral hearing loss for 4 years prior to his operation. All the data reported for JC (albeit incomplete) were obtained while he wore a mini speech processor with 17 active electrodes programmed in a bipolar stimulation mode (ie, electrodes 1 through 4 were not activated).

Experimental Design. Single-subject experimental designs have been reported to be appropriate for investigating the effects of treatment programs in communicative disorders.[16-19] First, the design allows the experimental exploration of functional relationships between an independent variable and the dependent variable. This type of controlled evaluation can demonstrate that the treatment, and not other extraneous variables, is responsible for a change in performance.[16,17] Moreover, single-subject designs make it possible to explore and control for intersubject variability.[17,18] This is particularly important for investigations that address issues related to the benefit of aural rehabilitation programs for cochlear implant recipients, since there is a large variability in performance among recipients and thus the specific postimplant rehabilitative needs of the recipients may differ substantially. Also, the design allows the exploration of intrasubject variability.[7,17] Finally, single-subject designs make possible the experimental investigation of issues that would be difficult to investigate by using group experimental designs. For example, it would be difficult to recruit the required number of cochlear implant recipients (homogeneous in terms of preimplant and postimplant speech perception performances) who would volunteer to take part in a long-term study to investigate the effects of the postimplant rehabilitation program. Thus, single-subject designs are efficient in terms of the time required to conduct the

TABLE 1. AURAL REHABILITATION PROGRAMS FOR EACH SUBJECT

Subject JC
- Consonant and vowel recognition (confusions) with stimuli presented audio-only, visual-only, or audiovisually
- Overlearned speech with contextually and noncontextually related sentences presented either audio-only or visual-only
- Related and unrelated sentences with clue words, presented audio-only or visual-only
- Advanced interactive stories presented either audio-only or visual-only
- Speech-tracking, presented audio-only or visual-only
- Twenty questions (in which clinician could ask 20 questions to identify topic selected by subject) with stimuli presented either audio-only or visual-only
- Basic instructions and practice regarding telephone use and telephone code
- Interactive telephone practice
- Some information sessions and activities stressing communication strategies[22]
- Speech Perception of Auditory Contrast Test[23] presented either audio-only or visual-only

Subject AR
- Consonant and vowel recognition (confusions) with stimuli presented either audio-only or visual-only
- Sentence identification by stress pattern, presented audio-only or audiovisually
- Related sentence recognition with linguistic and contextual clues, presented either audio-only or audiovisually
- Natural conversations in various simulated settings (performed audiovisually)
- Speech-tracking, with stimuli presented either audiovisually or audio-only
- Basic instructions and practice regarding use of telephone and telephone code
- Some information sessions and activities stressing communication strategies[22]

Subject RO
- Consonant and vowel recognition (confusions) completed mostly in audio-only condition
- Question/statement discrimination with stimuli presented in audio-only condition
- Easy and advanced interactive stories with stimuli presented in audio-only condition
- Related sentence recognition and unrelated sentence recognition with stimuli presented audio-only or audiovisually
- Closed-set and open-set word recognition with stimuli presented either audio-only or visual-only
- Natural conversations in various simulated settings (mostly audio-only)
- Basic instructions and practice regarding telephone use
- Interactive telephone practice with emphasis on telephone strategies
- Speech-tracking, initially in all three sensory modalities but rapidly emphasizing audio-only condition

Subject KF
- Consonant and vowel recognition (confusions) completed mostly in audio-only condition
- Closed-set and open-set word recognition with stimuli presented either audio-only or visual-only
- Related sentence recognition completed either audio-only or audiovisually
- Twenty questions presented either audio-only or visual-only
- Natural conversations in various simulated settings completed mostly in audio-only modality
- Basic instructions and practice regarding telephone use (eg, basic strategies for emergency telephone calls)
- Interactive telephone practice
- Speech-tracking, completed primarily in either audio-only or audiovisual modality
- Some information sessions and activities stressing communication strategies[23]

Unless otherwise specified, training activities were selected from (or based upon) *Nucleus 22 Channel Cochlear Implant System: Rehabilitation Manual.*[6]

investigation, and since they require fewer subjects, they are economical in cost.[19]

A staggered multiple baseline repeated single-subject experimental design was used in the present investigation (Fig 1). Staggering the introduction of the treatment (ie, the intensive aural rehabilitation program) made it possible to differentiate the effects of the postimplant aural rehabilitation program on speech perception from the improvements in speech perception due to practice (experience) with the sensory input provided by the device. The multiple baseline measures were provided by the results of a battery of speech perception tests that were administered in more than one sensory modality, including a visual-only condition (in which it was anticipated that the effects of the sensory device would be minimal). Thus, it was possible to use a subject's performance on the control conditions as a basis for comparison with the results obtained on other tests deemed to be relevant to the issues in the present investigation (ie, the audio-only and the audiovisual test conditions). The testing schedule was such that the subjects were tested once before their cochlear implant operations (ie, the baseline condition) and at 3-month intervals over a period of approximately 12 months postimplantation. Finally, the single-subject design made it possible to control for intersubject variability.

Test Protocol. The test protocol was selected to represent a wide variety of speech perception skills, progressing from very analytic tasks to tests that required a greater amount of synthetic speech perception ability. The following tests were included in the test protocol: the Consonant Recognition Test (J.-P. Gagné, R.C. Seewald, J. Stouffer, unpublished presentation, 1987), the Medial Vowel Test,[20] the Sentence-Understanding Without Context Test,[20] and Continuous Discourse Tracking (CDT).[21] Each test was administered in three different sensory modalities: audio-only, visual-only, and audiovisual.

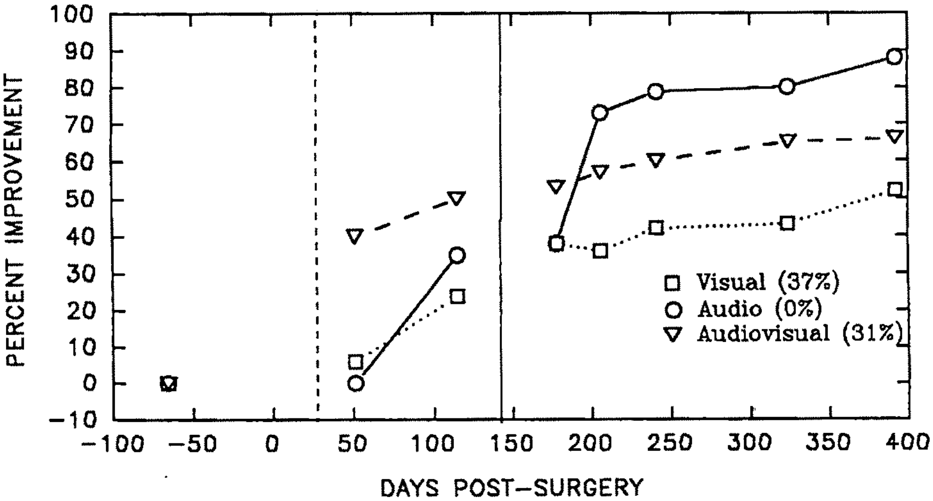

Fig 2. Percent improvement scores (total words) on Sentence-Understanding Without Context Test[20] are plotted as function of days postimplant for subject KF. Actual scores obtained during preimplant test session (ie, baseline scores) are provided in key. Dashed vertical line — day of initial hookup with speech processor, solid vertical line — introduction of intensive aural rehabilitation program.

All the tests were administered and scored according to the test procedures outlined by their respective authors. The subjects were tested individually. All the tests were administered in random order.

Aural Rehabilitation Training Program. An individualized postimplant aural rehabilitation program was developed for each subject. Essentially, the individualized programs followed the procedures recommended in the *Nucleus 22 Channel Cochlear Implant System: Rehabilitation Manual*[6] (hereinafter referred to as the Nucleus manual). Initially (ie, the day of the initial hookup of the speech processor and the following 2 days), the audiological intervention focused on defining the optimal cochlear implant map for the subject and providing informational counseling concerning the basic orientation, use, and maintenance of the cochlear implant device. Then, depending on their assigned treatment schedules, the subjects were seen biweekly or monthly to adjust their map and discuss general issues concerning the cochlear implant. These consultations were continued until the intensive aural rehabilitation phase of the project was introduced or until the counseling and adjustment services were no longer required. The subjects did not participate in any systematic speech perception training activities during this phase of the project.

All the subjects took part in an intensive aural rehabilitation program according to their preassigned treatment schedule. The program consisted of 12 weekly 3-hour sessions. The activities included in the intensive aural rehabilitation program focused primarily on speech perception training activities. The selection of the speech perception training activities was based on the following criteria: 1) the subject's performance on screening tests,[6] 2) the subject's expressed interest and needs, and 3) the clinician's assessment of the subject's strengths and weaknesses. Most of the training activities were selected from (or based upon) the Nucleus manual.[6] An overview of the specific training activities completed by each subject is provided in Table 1.[6,22,23]

RESULTS

The results obtained from individual subjects were analyzed separately. An example of the graphic displays used to summarize a subject's performance on each speech perception test is shown in Fig 2.[20] The results obtained were plotted as percent improvement scores. The percent improvement score was the difference between the score obtained during a given test session and the score obtained during the preoperative test session. (The actual preoperative test scores are reported in the figure key.) The two vertical lines that bisect the data show the day of the initial hookup (the dashed vertical line) and the day on which the subject started the intensive speech perception training program (the solid vertical line).

To determine whether the improvements in performance (if any) displayed by a subject on a given speech perception test could be attributed to the treatment program, we analyzed separately the results obtained during the pretreatment period and the results obtained during the posttreatment period. Performance for the pretreatment period was assessed by comparing the subject's preoperative performance to the results obtained after the initial hookup period but before the introduction of the intensive speech perception training program. Performance for the posttreatment period was assessed by comparing the subject's performance during the period following the initial hookup and the results obtained after the introduction of the intensive aural rehabilitation program.

A visual analysis of the patterns of results obtained for a subject was used to summarize the data obtained during the pretreatment and the posttreatment periods. A number of coded symbols were developed (and operationally defined) to summarize the pattern of results displayed by each subject. (The symbols are shown in the footnote of Table 2.[20]) First, the data were coded by two independent judges, separately. Then, the two judges met to resolve any differences in the codes assigned for each test condi-

TABLE 2. SUMMARY OF PATTERN OF RESULTS OBTAINED FROM INDIVIDUAL SUBJECTS ON EACH TEST INCLUDED IN SPEECH PERCEPTION TEST PROTOCOL

	Pre–Aural Rehabilitation				*Post–Aural Rehabilitation*			
Test	*JC*	*AR*	*RO*	*KF*	*JC*	*AR*	*RO*	*KF*
Consonant Recognition								
Visual	?	↗,↑	—	—	↔	—	↔,↗	—
Audio	?	↗,↑	↗,↑	↗,↑	↑	—	↔	—
Audiovisual	?	—	↗,↑	↗,↑	↗,↑	—	↔	↔,—
Visemes								
Visual	?	↑	T	↗,↑	↑	—	T	T
Audiovisual	?	↑	T	↗,↑	↗	—	T	T
Medial Vowel Test[20]								
Visual	?	—	—	—	—	—	—	—
Audio	?	↗,↑	↗,↑	↗,↑	↑,—	—	↗	↑,—
Audiovisual	?	—	—	↗,↑	—	↗	—	—
Sentences Without Context[20]: key words								
Visual	?	↔	↗,↑	↗,↑	↗	↑	T	—
Audio	?	↔	↗,↑	↗,↑	T	↑	T	↑,—
Audiovisual	?	↑	↗,↑	↗,↑	T	↑	T	T
Sentences Without Context[20]: total								
Visual	?	↔	↗,↑	↗,↑	↗	↗	T	—
Audio	?	↑	↗,↑	↗,↑	↑,T	↔	T	—
Audiovisual	?	↑	↗,↑	↗,↑	↑,T	↔	T	T
Tracking[21]								
Visual	?	↔	↔	↔	↗	—	↔	↗
Audio	?	↔	↔	↔	↑,—	—	↗	↔,↑
Audiovisual	?	↑	↑	↑	↑,—	↑,—	↗	↗

↑ indicates increase in performance, ↗ indicates increase in rate of improvement, ↔ indicates no further increases in rate of improvement, — indicates plateau or asymptotic performance, T indicates no change in rate of improvement due to ceiling effect, ? indicates insufficient data to assess pre–aural rehabilitation performance.

tion.

A summary of the patterns of results displayed by the individual subjects, on each of the tests included in the test protocol, is provided in Table 2.[20,21] (It was not possible to include all of the scores generated and used for the data analysis in the present report. Copies of the results [ie, scores] obtained from the individual subjects on each of the speech perception tests can be obtained by contacting J.-P. Gagné.) The results that are of particular interest to the present investigation were 1) increase in performance, 2) increase in the rate of improvement between the pretreatment and posttreatment periods, and 3) no further increase in the rate of improvement between the pretreatment and posttreatment periods. An example of results that illustrate an increase in performance is shown in Fig 2. When the Sentence-Understanding Without Context Test was administered in the audio-only condition, subject KF displayed significant improvements in key word recognition scores during the pretreatment period. The subject displayed further improvements on the same test during the posttreatment period. An example of results that illustrate an increase in the rate of improvement between the pretreatment and posttreatment periods is provided in Fig 3.[21] The CDT rates obtained for subject RO (displayed in the third panel) show an increase in the rate of improvement when the stimuli were presented in an audio-only mode. This result is indicated by the increase in the slope of the performance curve during the posttreatment condition. Finally, an example of results that illustrate continued improvements without any increase in the rate of improvement between the pretreatment and posttreatment periods is shown in Fig 4. The pre– and post–aural rehabilitation results obtained for subject RO did not reveal any appreciable differences in the slope of the performance curves for the audio-only (and audiovisual) modes on the Consonant Recognition Test.

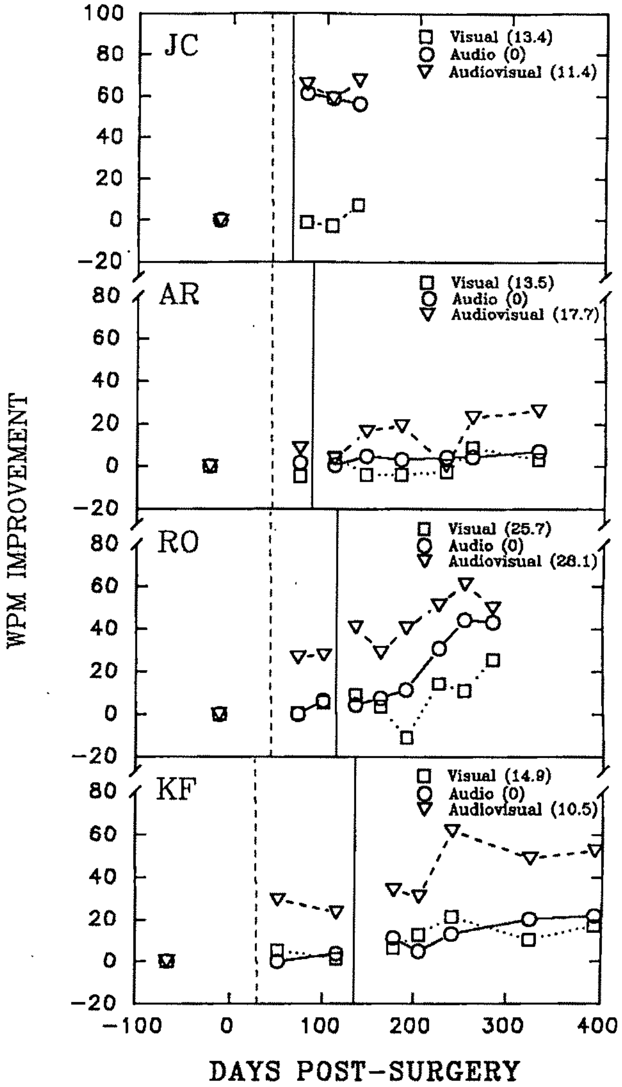

Fig 3. Improvement scores in words per minute (WPM) on Continuous Discourse Tracking[21] task are plotted as function of days postimplant. Each panel displays performance of one subject (identified in top left corner of panel). Actual scores obtained during preimplant test session (ie, baseline scores) are provided in key. Dashed vertical line — day of initial hookup with speech processor, solid vertical line — introduction of intensive aural rehabilitation program.

Table 2 reveals that all the subjects displayed improvements on some aspects of audio-only and au-

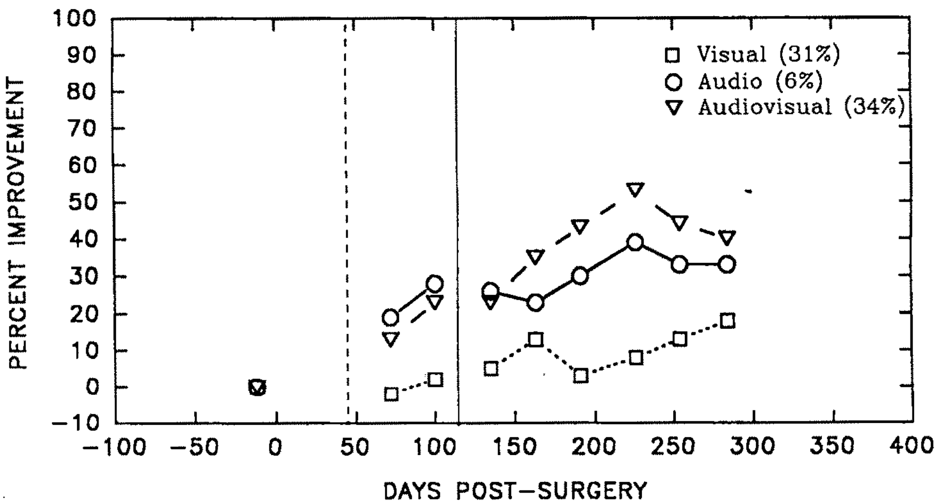

Fig 4. Percent improvement scores on Consonant Recognition Test are plotted as function of days postimplant for subject RO. Actual scores obtained during preimplant test session (ie, baseline scores) are provided in key. Dashed vertical line — day of initial hookup with speech processor, solid vertical line — introduction of intensive aural rehabilitation program.

diovisual speech perception following cochlear implantation. Except for CDT, there is no systematic evidence of improvements (or increases in the rate of improvement) among the four subjects following the introduction of the treatment. The results revealed that subject JC displayed significant improvements in speech perception performance following the introduction of the intensive aural rehabilitation program. It is not possible to discern whether those improvements are attributable to the rehabilitation program, since the program was started soon after the initial hookup with the speech processor. There are no test results available for the period of time between the initial hookup and the aural rehabilitation program for this subject. Thus, the post-aural rehabilitation improvements in performance cannot be unequivocally attributed to the effects of the aural rehabilitation program. In general, the performance of the other subjects showed no further systematic improvements (or increases in the rate of improvement) following the initial increases in performance observed once the subjects were fitted with their cochlear implants.

The subjects' performance on the CDT task is summarized in Fig 3. The results indicate that all of the subjects displayed some improvements (or an increase in the rate of improvement) during the post-aural rehabilitation period. Subject AR displayed some improvements in her audiovisual tracking rates. Three subjects (JC, RO, and KF) displayed some improvements (or an increase in the rate of improvement) in audio-only tracking rates. However, two of those subjects (JC and KF) also displayed post-aural rehabilitation improvements in their visual-only tracking rates. This latter finding was unexpected, since a scrutiny of the individual lesson plans for those two subjects indicated that most tracking activities conducted during the training program were completed in the audio-only and/or audiovisual sensory modality. The improvements observed in the CDT rates (in all three sensory modalities) may be due to extraneous factors such as 1) learning the task, 2) increased familiarity with the talker, and 3) the development of more efficient strategies by either the sender or the receiver. Previous reports have indicated that CDT may not be appropriate to evaluate the benefits of speech perception training.[24,25] Thus, it is not possible to attribute the improvements in audio-only and audiovisual CDT rates exclusively to the benefits provided by the rehabilitation program.

DISCUSSION

The results of the investigation demonstrated that cochlear implants improve speech perception abilities among the recipients. This finding is consistent with the findings of previous investigations.[1-5,7-13] Except for the results obtained for CDT, the improvements in speech perception scores were observed soon after the initial stimulation with the implant. These improvements are most likely attributable to the additional sensory input provided by the cochlear implant device. Also, the improvements in speech perception may be attributable to the everyday use, experience, and practice that the subjects had with the cochlear implant prior to their participation in the training program. On the basis of the results obtained in the present investigation, it was not possible to establish unequivocally that the postimplant improvements in speech perception were attributable to the program. These results are consistent with the findings of some previous reports that investigated the benefits of postimplant rehabilitation programs.[14,15] However, the present results do not agree with the findings reported by Lansing and Davis.[7]

Several factors could account for the present findings. First, it is likely that the test protocol was inadequate. The components of speech perception skills evaluated were limited by the tests included in the protocol. For example, informal inquiries revealed that the program provided two main benefits to the subjects: 1) improved telephone communication and 2) more effective use of communication strategies. Both of these aspects of verbal communication were included in the individualized programs (Table 1). However, none of the procedures included in the protocol evaluated those aspects of communication. Also, some tests included in the protocol may not have been sufficiently sensitive to reveal true changes in the performance of the subjects. For example, during the post–aural rehabilitation test sessions one subject (RO) displayed a ceiling effect on some of the tests (eg, viseme recognition, Sentence-Understanding Without Context, key words, and total word recognition scores).

Second, it could be argued that the audiologists may not have been effective. However, both audiologists were experienced and trained to provide rehabilitation services to adult cochlear implant recipients. (Except for subject RO, each subject received all of his or her postimplant audiological rehabilitation services from only one of the two audiologists. Subject RO, who displayed the most postimplant improvements on the speech perception tests, received services from both audiologists.) In addition, the individualized program designed for each subject was reviewed and discussed by at least two audiologist-members of the cochlear implant team (ie, J.-P.G., R.H., and M.L.). Also, the activities included in the programs were taken from (or based on) the Nucleus manual.[6] The stimuli and procedures for those activities are described in detail in the manual. It is unlikely that the present results could be attributed to the quality of services provided by the audiologists.

Third, the length of the aural rehabilitation services may have been too short to allow the subjects to display consistent improvements in speech perception. In the present investigation all the subjects completed approximately 36 hours of training. The length of the program was consistent with that of rehabilitation programs reported in the literature.[5,7,14,18]

Fourth, it could be argued that the activities included in the training program may not have been appropriate for the subjects. However, an individualized program was designed for each subject. The activities included were selected on the basis of the subject's performance on the screening tests developed for Nucleus 22-channel cochlear implant recipients.[6] Moreover, the training activities were chosen from the Nucleus manual,[6] and hence were an integral component of the present study of individuals who received Nucleus implants.

Finally, the results suggest that not every cochlear implant recipient will benefit from the training program used in the present investigation. This finding should not be taken as an indication that there is no need for a postimplant aural rehabilitation program. Subjects who demonstrate some specific difficulties integrating (decoding) the sensory information provided by the cochlear implant may benefit from some intensive speech perception training program. Also, subjects may benefit from intensive training on aspects of verbal communication that were not evaluated in the present investigation. For example, the subjects in the present investigation reported that they benefited from the training they received on communication strategies and telephone communication.

It is likely that all subjects will require some audiological rehabilitation follow-up services following cochlear implantation. For example, a certain amount of time and practice is required to complete the psychophysical tests that are used to determine the appropriate settings for the device (ie, the cochlear implant map and the stimulation mode). Changes in those settings, which occur frequently at first, may require modifications over a long period of time. Most cochlear implant recipients will require some basic informational counseling and orientation on the use, operation, and maintenance of the cochlear implant. The amount of informational counseling and the duration of the counseling period are likely to vary among clients. One approach that could be used to determine the appropriate amount and level of training would be to implement the same procedure(s) as those generally espoused for adults with an acquired hearing loss.[26-29] That is, the extent and the type of aural rehabilitation services provided to an individual should be based on the formulation of goals, established in consultation with the client, that would meet his or her specific needs. Based on the goals that are developed, aural rehabilitation activities and services should be provided to the client for a predetermined amount of time. Periodic evaluations should be scheduled to verify if the selected goals have been met and to determine when appropriate new goals should be set, previous goals should be reformulated, and aural rehabilitation services should be discontinued.[30]

CONCLUSION

It is not possible to reach a definite conclusion concerning the effects of intensive aural rehabilitation programs on the basis of the present findings. The basic premise of experimental research makes it impossible to accept the null hypothesis (in this case a conclusion that the rehabilitation program did not have an effect on the improvements in speech perception displayed by the subjects). However, the results of the present investigation support the findings of two previous investigations that concluded that intensive aural rehabilitation programs do not account for the postimplant improvements in speech perception.[14,15] However, as noted earlier, at least one previous investigation concluded that an intensive aural rehabilitation program did have some effects on the postimplant improvements on speech perception tests.[7] More research is needed to clearly delineate the effect of postimplant aural rehabilitation programs on speech perception.

ACKNOWLEDGMENTS — We thank M. Fey for his assistance with the research design and data analysis procedures, B. Bentley for her assistance with the data analysis and the preparation of the manuscript, and D. Greenaway for her comments on earlier drafts of the manuscript.

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COMPLICATIONS OF COCHLEAR IMPLANT SURGERY IN ADULTS AND CHILDREN

NOEL L. COHEN, MD RONALD A. HOFFMAN, MD
NEW YORK, NEW YORK

Surgery for cochlear prosthesis insertion exposes the patient to several potential risks. We review the surgical complication experience with cochlear implants in the United States. There have been no deaths attributable to these devices, few serious major complications, and relatively few minor complications. Major complications usually have to do with surgical technique and include flap necrosis, improper electrode placement, and rare facial nerve problems. Minor complications include dehiscence of incisions, infection, facial nerve stimulation, dizziness, and pedestal problems with the Ineraid device. Complications were less frequent in children than adults and were more likely to occur in the younger children than those above the age of 7 years. Complications were still fewer in groups of patients operated on within tightly controlled protocols. There was no increased incidence of otitis media in children who received the Nucleus Mini-22 device, and no reported sequelae from such otitis when it occurred.

KEY WORDS — cochlear implant, surgical complications.

INTRODUCTION

All surgery carries with it the risk of complications. This risk depends on multiple factors, which include the inherent difficulty and danger of a particular operation, the surgeon's operative skills, and the surgeon's experience with the operation being performed. The inherent risk of a particular operation is a reflection of the danger to surrounding structures, the delicacy of the maneuvers to be performed, critical dimensions of the anatomy, and the nature of any foreign body inserted into the patient. The presence of a large foreign body, for example, carries increased risk of contamination, infection, and tissue breakdown.

The operation for a cochlear implant consists of several steps of varying familiarity to the practicing otolaryngologist, otologist, and pediatric otolaryngologist-otologist. These are, in order of increasing complexity: mastoidectomy, posterior tympanotomy via the facial recess, creation of a large scalp flap, cochleostomy, and insertion of an electrode into the scala tympani (see Figure). All otolaryngologists who perform routine ear operations should be familiar with the anatomy and technique involved in creating a mastoid cavity. Many surgeons, however, are not proficient in the facial recess approach to the posterior mesotympanum. Moreover, in the common practice of otology, large scalp flaps are not often required. The head and neck surgeon may be more comfortable with these flaps than the average otolaryngologist or otologist. A large scalp flap is essential in covering the cochlear implant receiver stimulator. Flap design and execution are critical, and any lapse in technique may result in tissue breakdown with resultant loss of the implant.

A cochleostomy is unique to cochlear implant surgery, not being a part of any other commonly performed otologic procedure. The anatomy of the round window niche and the underlying scala tympani must be known to the operating surgeon in order to avoid a misplaced electrode. Finally, the insertion of an electrode into the scala tympani is also unique to this surgery, necessitating a high degree of dexterity and technical finesse, particularly in the instance of a partially obstructed or narrow scala tympani.

Intrinsic design characteristics of different cochlear implants impart specific potential risks. The size of a device, for example, can be a significant factor. Although the Nucleus Mini-22 device is considerably smaller than the older standard device, optimal insertion under the scalp of a child as young as 2½ years can be difficult, and routinely results in a considerable visible external deformity. While the flexibility of the Nucleus electrode array may make insertion into the scala tympani easier, the array being free to adapt to the curve of the cochlea, such flexibility increases the potential for kinking and compression. The Ineraid device, on the other hand, is smaller than the Nucleus, but has a percutaneous pedestal. This foreign body protruding through the scalp has the very real potential for irritation and infection. The Ineraid electrode array, while stiffer than the Nucleus, has spherical electrodes that protrude from the central axis of the array, impeding ease of insertion and making removal or repositioning difficult.

Young children are potentially more at risk as cochlear implant recipients than are adults because of the relatively small size of their skulls, lack of development of the mastoid, inevitability of otitis media, and the concern that future skull growth

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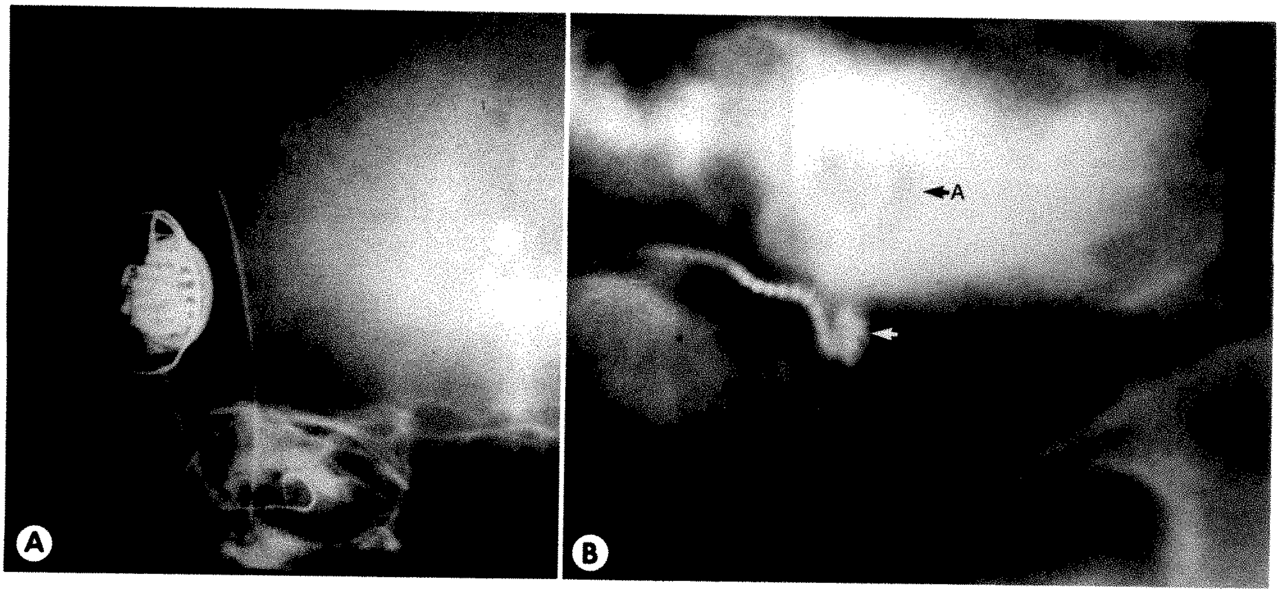
From the Department of Otolaryngology, New York University School of Medicine, New York, New York.

Presented at the Second International Cochlear Implant Symposium, Iowa City, Iowa, June 4-8, 1990.

REPRINTS — Noel L. Cohen, MD, NYU School of Medicine, 550 First Ave, New York, NY 10016.



Proper electrode placement. A) Cochlea. B) Electrode in hypotympanum (white arrow). A — position of cochlea.

will lead to movement of the implant receiver stimulator or electrode array.

METHODS

The surgical complications of cochlear implantation were reviewed in several groups of adults and one group of children. One hundred fifty-three adults received the Smith & Nephew Richards Ineraid device (formerly Symbion). Four hundred fifty-nine adults received the Nucleus standard or Mini-22 device. Three hundred nine children received the Nucleus implant. A final group consisted of 84 adult patients receiving one of three implants — the Nucleus, Symbion, or 3M/Vienna single-channel — as subjects in a Veterans Administration–sponsored randomized study.

Complications are divided into three categories: 1) adverse reactions, defined as postoperative complications resulting in a negative effect on the patient, 2) surgical complications, which are intraoperative, and 3) device-related problems, ie, those associated with mechanical failure of any part of the implanted device. Medical-surgical complications are further defined as major or minor. Major complications require additional surgery and/or hospitalization for treatment, while minor complications are those that are treated expectantly and/or with medication alone.

RESULTS

The three most common areas of reported surgical complication concern flap breakdown, electrode placement, and the Ineraid percutaneous pedestal. Flap problems ranged from relatively minor dehiscences to major loss of tissue requiring removal of the implant and surgical flap revision. Electrode problems ranged from minor kinking of the electrode to loss of a single ball electrode on the Ineraid array to compressed intracochlear electrodes and hypotympanic placement. Compressed and misplaced electrodes led to removal of the device and reimplantation. Pedestal problems ranged from minor itching to infection requiring replacement of the device.

There were no life-threatening complications in 153 Ineraid implantations (Table 1; personal communication, 1989, K. Dankowski, Smith & Nephew Richards). Twelve major complications occurred (7.8%), while there were 28 minor complications (18%). The minor complications were all mild to moderate pedestal inflammation or infection. Parkin[1] has graded pedestal reactions as class 1 to 5 and has recently reported on his experience with 35 patients. Pedestal itch or irritation was found in 32% of the 35 patients at 6 months, but decreased to 12% between 24 and 36 months and to 7% between 36 and 48 months. On the other hand, the rate of infection about the pedestal remained constant at 5% between 18 and 24 months and 6% between 36 and 48 months.

There were 12 major pedestal problems requiring explantation among the 153 Ineraid implants: five pedestals became infected, two pedestals suffered fractures, there were three device failures, one patient was nonstimulable, and one patient had an ossified cochlea that precluded electrode insertion.

TABLE 1. INERAID COMPLICATIONS (N = 153)

Major (all explanted)		12
Infection	5	
Trauma	2	
Device failure	3	
Ossified cochlea	1	
Nonstimulable	1	
Minor (pedestal inflammation)		28

TABLE 2. TOTAL COMPLICATIONS WITH NUCLEUS DEVICE (N = 459)

Major	
Scalp breakdown, removal of implant	9
Compressed electrode	4
Incorrect electrode position	4
Perilymph fistula	3
Exposure of mastoid bowl electrode	1
Severe seventh nerve stimulation, implant removed	1
Meningitis*	1
Total	23
Minor	
Local treatment of flap problem	16
Seventh nerve weakness with recovery	8
Minor seventh nerve stimulation, programmed out	3
Minor change of taste	2
Transient dizziness without diagnosis	2
Tympanic membrane perforation with healing	1
Total	32

Reprinted from Cohen et al.[2]

*Life-threatening; considered here as major complication.

Six of these 12 devices were replaced with another Ineraid device, and 3 with the Nucleus device, and three patients had no second device inserted.

Another complication unique to the Ineraid device is the exposure of the pedestal bone-anchoring screws. Although there are eight holes in the pedestal, typically only four or five screws are inserted at operation. Screw exposure is the result of retraction of skin from the edges of the pedestal post. This, in turn, gives rise to granulation tissue and inflammation or infection. If these are not responsive to conservative medical management such as cauterization and the use of topical and oral antibiotics, additional treatment with intravenous antibiotics may be required. In extreme cases, there may be a need for removal of one or more screws and possible flap revision. Seventeen of 612 (2.6%) bone screws placed in 153 patients had to be removed (personal communication, 1989, K. Dankowski, Smith & Nephew Richards).

We previously reported surgical complications that resulted from 459 Nucleus device operations in adult patients in North America (Table 2).[2] These operations were performed by 108 surgical teams. There were 55 medical or surgical complications, for an overall rate of 11.9%. Of these, 23 (5%) were major complications and 32 (7%) minor complications. The major complications included one life-threatening case of meningitis, which resolved under treatment, and no deaths.

There were eight electrode problems, consisting of either compressed arrays or hypotympanic placement (1.7%). Ten patients required removal of their device, with or without reimplantation: eight patients with electrode problems, one with seventh nerve stimulation and no auditory response, and one whose electrode array became exposed in a radical mastoid cavity.

TABLE 3. COMPLICATIONS IN CHILDREN BY AGE (N = 179)

Age (y)	*Complication*
2-3	4.8%
4-6	2.5%
7-10	1.8%

There were data in this study to suggest that there is a learning curve among surgeons performing cochlear implant surgery. There was a higher incidence of complications with the older "standard" device (14.5%) than the Mini device (8.2%). This may reflect the fact that many surgeons started their experience with the standard device and then followed with the Mini. However, the standard device was thicker and may have contributed to a more frequent complication rate, especially in terms of flap necrosis, which occurred in 6.5% of those with the standard device but only 3.8% of those who received the Mini. Surgeons who had prior experience with the standard device had a complication rate with the Mini device of 8.4%, while those who started with the Mini device had a complication rate of 19%. Eighty percent of the flap complications occurred within the first three operations done by an individual surgeon. Finally, although not statistically significant, surgeons who attended the Nucleus surgical training course had a lower complication rate than those who did not.

In a group of 309 children who received Nucleus cochlear implants in North America, there were no deaths, no life-threatening complications, 12 (3.9%) major complications, and 9 (2.9%) minor complications (personal communication, 1989, S. Staller, Cochlear Corp). These 309 operations were performed by 25 surgical teams, all of which had experience with this device in adults prior to operating on their first child. The total complication rate of 6.8% compares favorably with the adult rate of 11.9%, while the major complications were 3.9% in children and 5% in adults. The minor complication rate was considerably higher in adults, 7% versus 2.9%, accounting for much of the difference between the two groups. The incidence of flap complication was only 2% in the pediatric population, and there was but one hypotympanic electrode placement. This may reflect the greater experience of surgeons performing pediatric cochlear implants. The incidence of complications was lower in children over the age of 7 (Table 3).

The Cochlear Corporation surveyed the incidence of otitis media in 133 children implanted in North America (S. Staller, A. Beiter, J. Brimacombe, unpublished observations, 1989). One hundred thirty-three questionnaires were sent, with 131 responses. Seventeen children (13%) suffered from at least one episode of acute otitis media. Fourteen of these children were under 10 years of age. Seven had otitis in both ears. Two had otitis in the implanted ear only, and five in the nonimplanted ear only. Hence, there was a lower incidence of infection in the implanted ear, and there were no adverse sequelae.

As part of a national cooperative study funded by the Department of Veterans Affairs, 84 patients were randomized to one of the following three implants: the Smith & Nephew Richards Ineraid multichannel device, the Nucleus multichannel device, or the 3M/Vienna single-channel device. There were no life-threatening complications, three relatively insignificant major complications, and nine minor problems. There were no cases of flap necrosis, no compressed or hypotympanic electrodes, and no seventh nerve palsies. Four patients required reoperation, one owing to a Vienna device failure, one to a Vienna device that produced seventh nerve stimulation to the detriment of auditory stimulation, one to an Ineraid pedestal fracture, and one to an Ineraid pedestal infection (included in data on above 153 Ineraid patients).

DISCUSSION

As with all surgical procedures, complications are inevitable with cochlear implantation. Moreover, there is a learning curve, with larger numbers of operations being performed by smaller numbers of surgeons, resulting in a lower incidence of operative and postoperative problems.

Although life-threatening complications are extremely rare, the devastating effects of major flap breakdown, facial palsy, or incorrect electrode placement cannot be underestimated. Major flap breakdown leads to device contamination and the need for intravenous antibiotics and/or surgical revision. Multiple operations are sometimes required. The trauma of facial paralysis is well known to all otolaryngologists. Faulty electrode placement results in lack of auditory response, a particularly devastating outcome for a patient anticipating hearing restoration. Patients suffer physically, financially, and psychologically.

What can be done to further diminish the complication rate from cochlear implant surgery? Surgeons must familiarize themselves with the unique aspects of this operation. Emphasis must be placed on attendance at a device-specific training course in order to provide experience with the unique aspects of a particular implant and with the necessary surgical maneuvers, particularly cochleostomy and electrode insertion. Videotapes and readings are viewed as supplemental to a device-specific training course.

It is strongly recommended that a transorbital radiograph be performed before removing the patient from the operating room table in order to document and ensure proper electrode position (see Figure).

Finally, it is desirable that those surgeons without prior experience either participate in an operation or avail themselves of the presence of a more experienced surgeon when performing their first implant. In so doing, it should be possible to lower the complication rate of this complex surgery to a minimum while respecting our patients' desire to choose their physician and optimize their medical care.

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HISTOPATHOLOGIC CORRELATION OF SPIRAL GANGLION CELL COUNT AND NEW BONE FORMATION IN THE COCHLEA FOLLOWING MENINGOGENIC LABYRINTHITIS AND DEAFNESS

JOSEPH B. NADOL, JR, MD WENCHONG HSU, MD

BOSTON, MASSACHUSETTS

Bacterial meningitis is a common cause of profound deafness and, hence, a common cause of deafness in published series of patients treated with a cochlear prosthesis. Labyrinthitis ossificans is a common finding in meningogenic labyrinthitis and has been considered a relative contraindication to cochlear implantation. In the present study, the numbers of remaining spiral ganglion cells in cases of meningogenic labyrinthitis were correlated with the severity of new bone formation within the inner ear. Six temporal bones in which profound sensorineural hearing loss occurred in life secondary to meningogenic labyrinthitis were studied by serial section light microscopy. Some degree of labyrinthitis ossificans was found in four of six. There was a moderately strong negative correlation between the number of years of total deafness and the percentage of normal of the remaining spiral ganglion cell count. There was a strong negative correlation between the degree of bony occlusion by labyrinthitis ossificans and the normality of the spiral ganglion cell count. The percentage of bony occlusion of the membranous labyrinth increased with the years of total deafness. The significance of these findings for cochlear implantation of individuals with meningogenic labyrinthitis is discussed.

KEY WORDS — bacterial meningitis, cochlear prosthesis, deafness, histopathology, labyrinthitis ossificans, spiral ganglion.

INTRODUCTION

Bacterial meningitis is a common cause of deafness in both children and adults and, hence, is a common cause of deafness in published series of patients treated with the cochlear prosthesis. It has been estimated that 8% to 24% of cases of profound deafness in school-aged children are due to bacterial meningitis.[1-4] In individuals over the age of 2½ years, some degree of sensorineural hearing loss was found in 21% of survivors of bacterial meningitis.[5] Of these, 8% had a total loss of hearing in one or both ears. Approximately 2% to 5% of children and adults who survive bacterial meningitis develop a profound bilateral sensorineural hearing loss.[5-7] In a series of 128 children with profound deafness treated with cochlear implantation, 64% were deafened by bacterial meningitis.[8]

Labyrinthitis ossificans, or new bone formation within the cochlea, is a common finding in meningogenic labyrinthitis. Eisenberg et al[9] reported that 20 of 25 children with meningogenic deafness treated by cochlear implantation had some degree of ossification identified by radiography and confirmed at operation. Of these, the degree of ossifica-

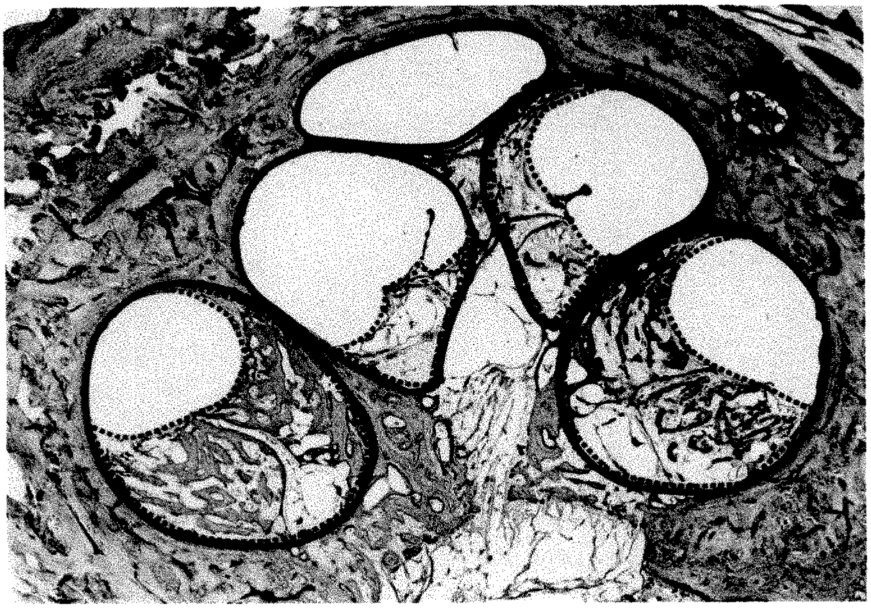

Fig 1. (Case 3) Midmodiolar section of right cochlea from individual deafened by bacterial meningitis 83 years prior to death (H & E, original x25). Percentage of bony occlusion of membranous labyrinth was calculated by dividing area of new bone formation (dashed line) by area of normal membranous labyrinth (solid line).

From the Department of Otology and Laryngology, Harvard Medical School, and the Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts. Supported by Cochlear Implant Project Grant P01-DC00361.

Presented at the Second International Cochlear Implant Symposium, Iowa City, Iowa, June 4-8, 1990.

REPRINTS — Joseph B. Nadol, Jr, MD, Dept of Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.

TABLE 1. CORRELATION OF SPIRAL GANGLION CELL COUNT AND NEW BONE FORMATION IN MENINGOGENIC LABYRINTHITIS

Case	*Age*	*Years Deaf*	*Segment*	*SPG Count*	*% Normal SPG Count*	*% Bony Occlusion*
1	78	23	1	1,602	51	0
			2	5,841	75	0
			3	3,933	94	0
			4	3,915	67	0
			Total	15,291	73	0
2	70	69	1	3,465	89	45
			2	4,275	44	4
			3	2,475	48	0
			4	2,655	37	0
			Total	12,870	50	9
3	84	83	1	261	9	98
			2	819	12	63
			3	279	7	40
			4	171	3	22
			Total	1,530	8	52
4	49	48	1	1,044	25	35
			2	5,166	50	4
			3	2,628	47	0
			4	2,385	30	0
			Total	11,223	40	6
5	54	40	1	3,033	81	43
			2	5,265	57	25
			3	3,636	73	6
			4	3,285	47	0
			Total	15,219	61	17
6	1.5	1.5	1	2,340	42	0
			2	8,586	63	0
			3	5,265	71	0
			4	5,112	49	0
			Total	21,303	58	0

SPG — spiral ganglion cell.

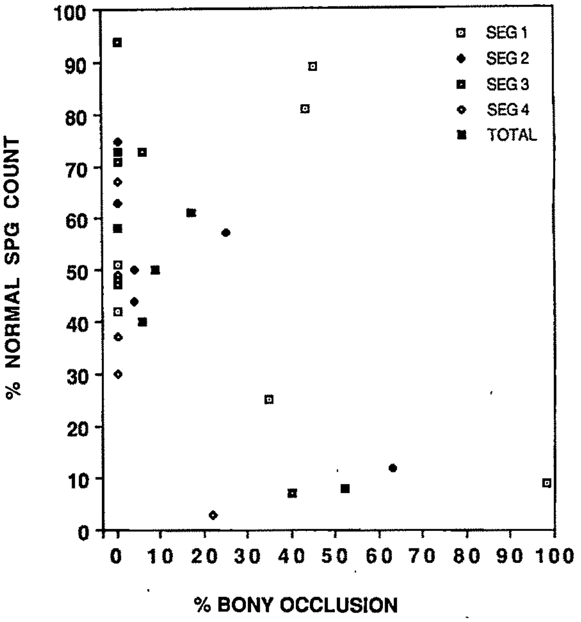

Fig 2. Scattergram correlating percentage of normal of spiral ganglion cell (SPG) count by segment and total count with percentage of bony occlusion in six cases of meningogenic labyrinthitis.

tion was severe in 6. Balkany et al[10] reported that of 105 patients with cochlear implants, 15, or 14%, had new bone formation identified at operation. Of these 15 cases, 7 were caused by meningitis.

Although labyrinthitis ossificans has been considered a relative contraindication to cochlear implantation,[11] several recent reports have demonstrated successful electrical stimulation despite the presence of new bone formation found within the inner ear at operation.[1,10,12] Thus, in the series reported by Balkany et al,[10] electrical stimulation of the auditory nerve was possible in 14 of 15 patients; and in 9 of 15, or 60%, open-set speech discrimination was achieved. In the series of Eisenberg et al,[9] electrical stimulation was achieved in 19 of 20 patients implanted despite labyrinthitis ossificans. Electrical stimulation was not achieved in 1 patient with severe new bone formation.

Although not all the determinants of success in achieving useful electrical stimulation of the auditory nerve with the cochlear prosthesis are known, the number of surviving and functional spiral ganglion cells is considered important.[13,14] In a series of temporal bones from patients with profound deafness, ears deafened by bacterial meningitis and labyrinthitis have among the lowest numbers of surviving spiral ganglion cell counts.[14,15] The purpose of the present study was to evaluate the correlation of the numbers of remaining spiral ganglion cells and the severity of new bone formation caused by meningogenic labyrinthitis.

MATERIALS AND METHODS

In the human temporal bone collection at the Massachusetts Eye and Ear Infirmary, there were nine temporal bones from six patients who in life suffered profound sensorineural hearing loss due to bacterial meningitis. Of the three patients who were bilaterally deafened, one temporal bone was selected at random for inclusion in the study, for a total of six temporal bones from six patients in this series.

All temporal bones were fixed in Heidenhain Susa solution, decalcified in trichloracetic acid, and embedded in celloidin. The temporal bones were sectioned at a thickness of 20 μm in the horizontal plane, and every 10th section was stained with hematoxylin and eosin and mounted on glass slides. The spiral ganglion was graphically reconstructed by a method described by Schuknecht[16,17] and Otte et al.[14] All ganglion cells with visible nucleoli were counted on every 10th section. Counts were multiplied by 10 to account for unmounted sections and by a correction factor of 0.9 to account for doubly counted spiral ganglion cells.[17] Ganglion cell populations were determined for each of four segments of the spiral ganglion (0 to 6 mm, 7 to 15 mm, 16 to

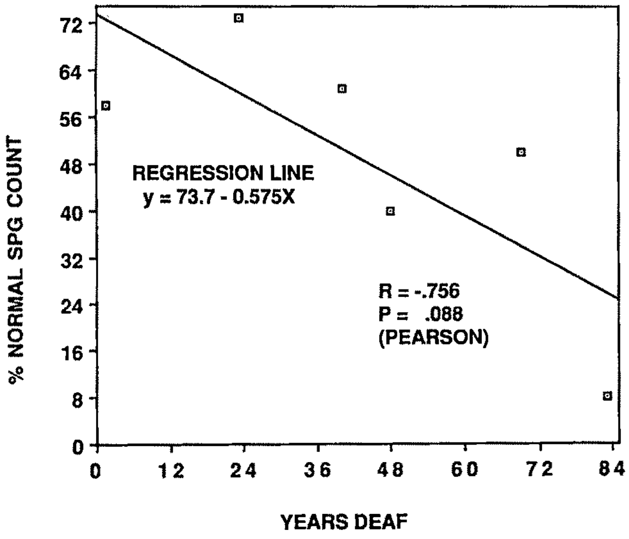

Fig 3. There was negative correlation between percent of normal spiral ganglion cell (SPG) count and number of years of total deafness.

22 mm, and 23 mm to apex), and spiral ganglion cell counts in each of the four segments were added to achieve a total spiral ganglion cell count for each temporal bone.

To quantify the severity of labyrinthitis ossificans a percentage of the area of the membranous labyrinth replaced by new bone was measured by means of computer-assisted morphometry (Fig 1). The percentages calculated for each 10th section in each of the four segments of the cochlea were averaged to achieve a percentage occlusion of the membranous labyrinth for each segment. An approximation of the degree of bony obliteration of the entire cochlea was determined by a weighted average of each of the segmental averages, based on segmental and total cochlear lengths. The segmental and total spiral ganglion cell counts were divided by corresponding counts in published age-matched controls[14] to determine the percent normality of counts of remaining spiral ganglion cells. The resultant data base is presented in Table 1.

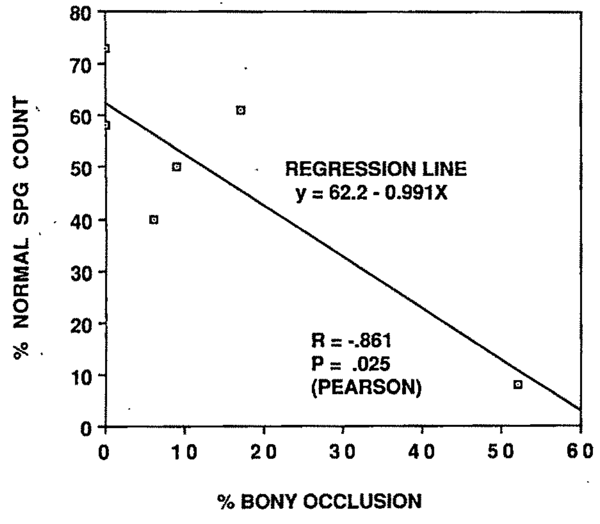

Fig 4. There was negative correlation between percent of normal spiral ganglion cell (SPG) count and percent of bony occlusion.

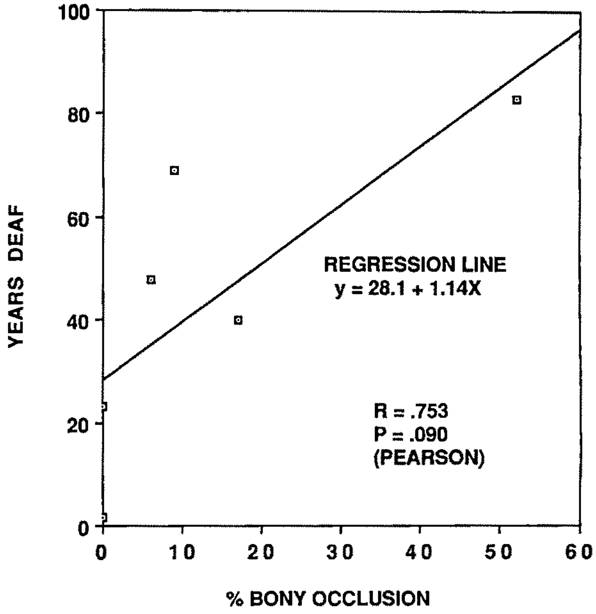

Fig 5. There was positive correlation between percent of bony occlusion and number of years of total deafness after meningogenic labyrinthitis.

For statistical analysis, segmental and total spiral ganglion cell counts, degree of bony occlusion by labyrinthitis ossificans, and the number of years that the individual was totally deaf prior to death were correlated by means of the BMDP statistical software package with use of the Pearson correlation.

RESULTS

The histopathologic data base generated from six ears profoundly deaf during life from six individuals is presented in Table 1. Of the six temporal bones with meningogenic labyrinthitis, some degree of labyrinthitis ossificans was found in four. A scatterplot of segmental and total spiral ganglion cell counts expressed as a percentage of normal and the degree of new bone formation for each segment and the entire cochlea is presented in Fig 2. In all cases in which the segmental and total bony occlusion was less than 10%, at least 30% of the normal segmental and total spiral ganglion cell count was found. With few exceptions, the lowest spiral ganglion cell counts were found in segments with the most severe bony occlusion by labyrinthitis ossificans. Scatterplots correlating the percent normality of the spiral ganglion count with the years deaf, the percent normality of the spiral ganglion count with the percent bony occlusion, and the number of years deaf with the percentage of bony occlusion of the membranous labyrinth are presented in Figs 3, 4, and 5, respectively.

Correlation of Spiral Ganglion Cell Count With

TABLE 2. PEARSON CORRELATIONS FOR SEGMENTAL SPIRAL GANGLION CELL COUNTS AND DEGREE OF BONY OCCLUSION

	Pearson Correlation	
Segment	*r*	*p*
1 (0-6 mm)	−.30	.59
2 (7-15 mm)	−.84	.033
3 (16-22 mm)	−.79	.066
4 (23 mm to apex)	−.81	.049

Years Deaf. There was a moderately strong negative correlation between the number of years of total deafness and the percentage of normal of the total spiral ganglion cell count (Fig 3). Likewise, there was a strong negative correlation between the degree of bony occlusion by labyrinthitis ossificans and the normality of the spiral ganglion cell count (Fig 4). The percentage of total bony occlusion of the membranous labyrinth increased ($r = .753$, $p = .090$) with the years of total deafness (Fig 5).

Segment-Specific Correlations Between Percent Bony Occlusion and Percent of Normal Spiral Ganglion Cells. To test the hypothesis that there was a correlation between segmental bony occlusion and segmental spiral ganglion cell count, Pearson correlations were determined for each of the four cochlear and spiral ganglion segments. The Pearson correlations are presented in Table 2. Statistically significant correlations ($p < .05$) indicating the presence of fewer spiral ganglion cells when there is more bony occlusion were found for segments 2 and 4. For segment 3, there was a strong negative correlation ($r = -.79$), but it did not reach statistical significance ($p = .066$). The strength of the correlation was weakest for segment 1.

DISCUSSION

The data from histopathology of temporal bones from ears deafened by meningogenic labyrinthitis suggest that there is a moderately strong negative correlation between the spiral ganglion cell count and the degree of bony occlusion. This negative correlation is valid for the total cochlea and for at least two segments of the cochlea. The poor correlation seen in the basal turn (segment 1) may be accounted for by the fact that a variety of disease processes affecting spiral ganglion cells preferentially affect this turn. Since significant degrees of bony occlusion of the cochlea may be determined preoperatively by modern computed tomographic techniques, it is possible to predict that among patients deafened by meningogenic labyrinthitis, those with severe degrees of bony occlusion will have the lowest spiral ganglion cell counts. In addition, the data suggest that the degree of bony occlusion of the cochlea increases with the years elapsed from the time of total deafness induced by meningogenic labyrinthitis (Fig 5), suggesting that cochlear implantation done soon after confirmation of profound deafness caused by bacterial meningitis will be less impeded by new bone formation than when done years later.

Among patients deafened by meningogenic labyrinthitis, individuals who have been profoundly deaf for many years will have lower spiral ganglion cell counts than those recently deafened (Fig 3). However, it is important to remember that the minimum requisite number of functioning spiral ganglion cells and the optimal distribution along the cochlear length for these cells is as yet undetermined. The presence of significant numbers of spiral ganglion cells in meningogenic labyrinthitis, even in those with severe bony occlusion, is reason for cautious optimism that only very few patients affected by meningogenic labyrinthitis cannot achieve electrical stimulation using the cochlear prosthesis — a conclusion corroborated by previously reported clinical experience.[9,10,13]

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INTERNATIONAL HEARING AID CONFERENCE
GENERAL ANNOUNCEMENT AND CALL FOR PAPERS

An International Hearing Aid Conference will be held June 15-17, 1993, at The University of Iowa, Iowa City, Iowa. For information on registration and accommodation, contact the Conference Center, University of Iowa, Memorial Union, Iowa City, IA 52242; (319) 335-3231, Fax (319) 335-3407. For information on Call for Papers, contact Regina Tisor (319) 356-2471, Fax (319) 356-4547. We have applied for Continuing Education Units from ASHA and HAIC.

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THE DEAFNESS RESEARCH FOUNDATION
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The Deafness Research Foundation's Otological Research Fellowship will be sponsored by a department of otolaryngology conducting otological research. Where a unique opportunity exists in a related discipline, the fellowship may be conducted in that discipline while maintaining liaison with the department of otolaryngology. The fellowship would be scheduled as a one-year block of time at the end of the third year of medical school, thus requiring a one-year leave of absence from the medical school curriculum. The fellowship would be funded in the amount of $10,000, plus up to $3,500 for animals and consumable supplies. Applications for 1992 funding must be received by November 15, 1991. For more information, please contact Walter A. Petryshyn, MD, Medical Director, The Deafness Research Foundation, 9 East 38th Street, New York, NY 10016; (212) 684-6556.

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BILATERAL VOCAL FOLD MOTION IMPAIRMENT: PATHOPHYSIOLOGY AND MANAGEMENT BY TRANSVERSE CORDOTOMY

HASKINS K. KASHIMA, MD
BALTIMORE, MARYLAND

Although bilateral vocal fold paralysis (BVFP) is an uncommon disorder, bilateral vocal fold motion impairment (BVFMI) resulting from a variety of laryngeal derangements is encountered with increasing frequency. Moreover, pure BVFP accounts for only a small proportion of BVFMI. When antecedent factors associated with BVFP are absent, recognition of BVFMI is often delayed and frequently overlooked. The requirements for assessment and successful management of BVFMI are 1) recognition of its presence, 2) identification of the constituent factors restricting vocal fold motion, 3) objective assessment of airway patency, and 4) selection of a reliable management plan. More often than not, two or more BVFMI-causing factors are present; only rarely is BVFMI attributable to a single vocal fold motion–limiting cause. The clinical and endoscopic examinations should evaluate the relative contributions of vocal fold paralysis, cricoarytenoid joint fixation, infiltrative disorders, and webs and synechiae that cause restricted vocal fold motion. The flow-volume loop examination documents airflow rate and volume and the site, nature, and severity of the obstructing lesion(s). This presentation describes the evaluation and rationale for management in BVFMI. The surgical techniques currently used to address BVFMI are compared to determine their respective merits and drawbacks, depending upon the constituent factors causing vocal fold motion limitation.

KEY WORDS — arytenoidectomy, bilateral vocal fold paralysis, cordotomy, cricoarytenoid arthrodesis, infiltrative lesions of vocal folds, laryngeal web.

INTRODUCTION

Bilateral vocal fold paralysis (BVFP), encountered most often after thyroidectomy, is occurring with diminishing frequency. It constitutes a subset of bilateral vocal fold motion impairment (BVFMI), a syndrome that is encountered with increasing frequency in the contemporary medical care setting and that arises from a broad range of circumstances ranging from blunt or endoscopic laryngeal trauma to arthritis. Bilateral vocal fold motion impairment is often the solitary residual after successful treatment of an unrelated principal medical or surgical disorder. Moreover, because the index of suspicion is not high, diagnosis of BVFMI is frequently overlooked.

BILATERAL VOCAL FOLD MOTION IMPAIRMENT

The principal symptoms of BVFMI are dyspnea and voice impairment. Vocal fold flaccidity results in inward vocal cord displacement on forced inspiration, airway collapse, and flow rate limitation. Outward displacement of the vocal folds on expiration causes air wastage and light-headedness. The hypotonic vocal folds appose incompletely on phonation and produce a voice with reduced loudness and limited pitch range. These symptoms can be of variable severity depending, in part, upon degree of paralysis, whether complete or partial. The resulting chronic dyspnea and easy fatigability may masquerade as chronic fatigue syndrome.

There are four principal categories of BVFMI: 1) vocal fold paralysis, 2) cricoarytenoid joint fixation (CAJF), 3) vocal fold infiltrative lesions (VFIL), and 4) cicatricial webs. The foregoing categories occur singularly or in combination and either may result from a primary disorder (such as bulbar palsy causing paralysis, rheumatoid arthritis causing CAJF, amyloidosis causing VFIL, and mucosal pemphigoid causing cicatricial webs) or may have an iatrogenic basis such as after surgical dissection, endotracheal intubation and endoscopic instrumentation, laser dissection, infection, bleeding, and resultant fibrosis (Table 1).

TABLE 1. CATEGORIES AND CAUSES OF BILATERAL VOCAL FOLD MOTION IMPAIRMENT

- Bilateral vocal fold paralysis
  - Thyroidectomy
  - Parathyroidectomy
  - Neurologic disorders
- Midbrain stroke
- Amyotrophic lateral sclerosis
- Cricoarytenoid joint fixation
  - Rheumatoid arthritis
  - Blunt neck injury
- Vocal fold infiltrative lesions
  - Sarcoid
  - Amyloid
  - Postirradiation fibrosis
  - Wegener's granulomatosis
  - Lipoid granulomatosis
  - Idiopathic fibrosis
- Posterior glottic web
  - Prolonged endotracheal intubation
  - Cicatricial pemphigoid

From the Department of Otolaryngology–Head and Neck Surgery, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

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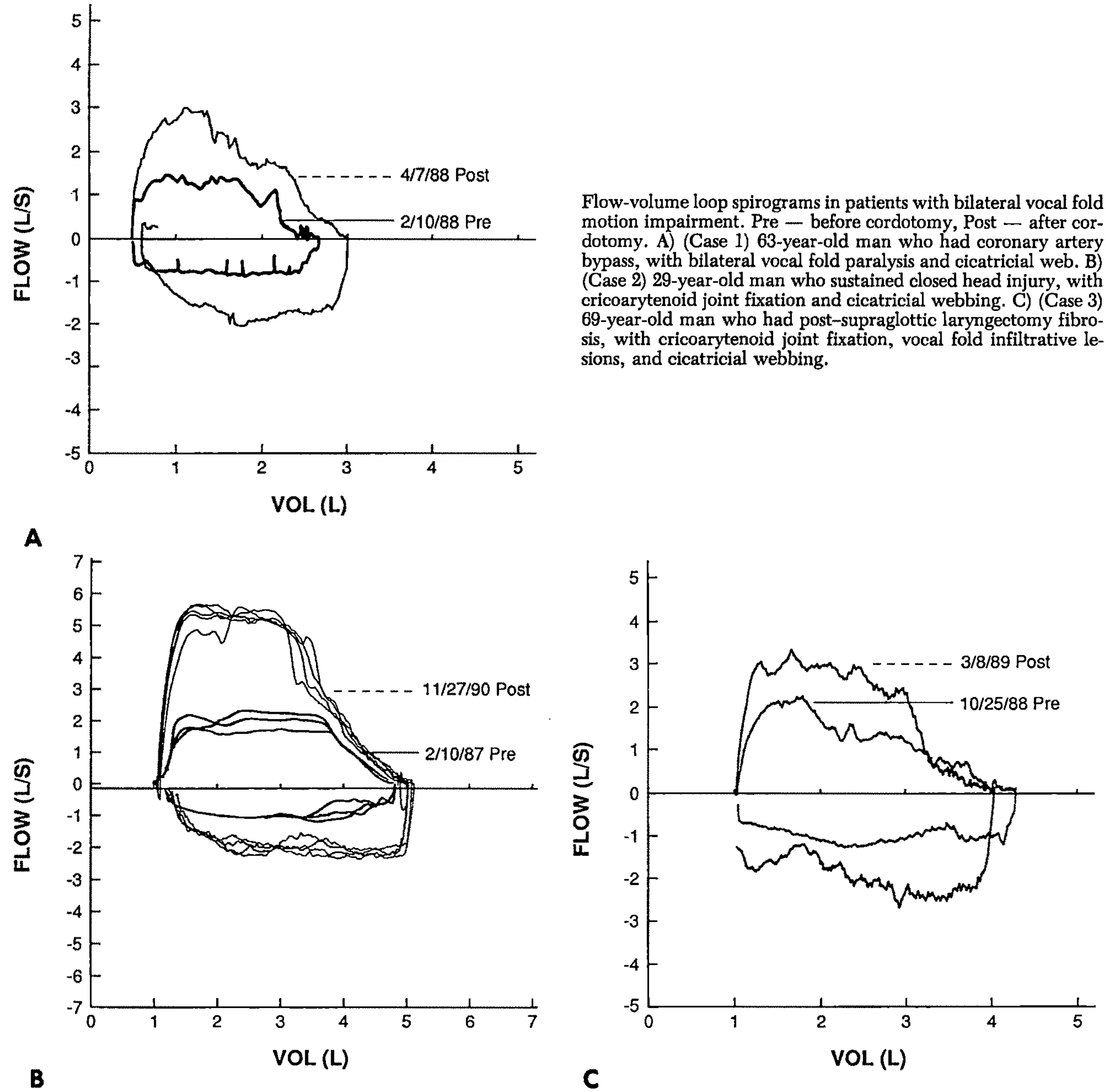
REPRINTS — Haskins K. Kashima, MD, Dept of Otolaryngology–Head and Neck Surgery, The Johns Hopkins Medical Institutions, 600 N Wolfe St, Carnegie Building Room 469, Baltimore, MD 21205.



Flow-volume loop spirograms in patients with bilateral vocal fold motion impairment. Pre — before cordotomy, Post — after cordotomy. A) (Case 1) 63-year-old man who had coronary artery bypass, with bilateral vocal fold paralysis and cicatricial web. B) (Case 2) 29-year-old man who sustained closed head injury, with cricoarytenoid joint fixation and cicatricial webbing. C) (Case 3) 69-year-old man who had post-supraglottic laryngectomy fibrosis, with cricoarytenoid joint fixation, vocal fold infiltrative lesions, and cicatricial webbing.

Cricoarytenoid joint fixation immobilizes the arytenoid cartilage, through which the action of the adducting and abducting muscles is transmitted. Passive mobility of the vocal cords is preserved, and passive mobility of the aryepiglottic folds, normally stabilized by the arytenoid, may be exaggerated; hence, inspiratory stridor tends to be conspicuous and voice impairment is less severe.

Infiltrative disorders such as amyloid, sarcoid, or fibrosis in the vocal folds abolish abduction and adduction in spite of intact neuromuscular function; vocal cord rigidity disallows passive displacement. Airway limitation and voice compromise tend to be severe.

Cicatricial webs inhibit abduction more than adduction so that airway compromise is more severe and voice impairment is usually minimal. Pure laryngeal paralysis abolishes voluntary abduction and/or adduction. Passive displacement of the vocal folds is greater than with CAJF, VFIL, or cicatricial webs; in paralysis of long standing, passive vocal cord excursion is exaggerated because of muscle atrophy. The above features are compounded when one or more inhibiting lesions coexist — a common occurrence. Postinflammatory reactive infiltration and cicatricial webs can be sequelae to laryngeal instrumentation and/or endotracheal intubation; such iatrogenic aftereffects compound the nature and severity of BVFMI.

Irrespective of the underlying dysfunction, BVFMI presents with a near-indistinguishable clinical picture. Differentiating the four categories of BVFMI

TABLE 2. FLOW-VOLUME LOOP SPIROGRAM VALUES BEFORE AND AFTER CORDOTOMY

		Expiration			*Inspiration*		
Patient	*Date*	*FVCE (L)*	*V̇Emax (L/s)*	*V̇E50 (L/s)*	*FVCI (L)*	*V̇Imax (L/s)*	*V̇I50 (L/s)*
1	Preoperative (2/10/88)	2.29	1.86	1.71	2.29	1.10	0.99
	Postoperative (4/7/88)	2.90	3.47	2.13	2.78	2.32	2.30
2	Preoperative (2/10/87)	4.54	4.08	3.94	4.15	1.86	1.74
	Postoperative (11/27/90)	4.33	5.92	5.33	4.07	2.56	2.28
3	Preoperative (10/25/88)	3.39	2.34	1.42	3.28	1.63	1.26
	Postoperative (3/8/89)	3.13	3.48	2.71	3.13	2.78	2.09

FVCE — forced vital capacity on expiration, V̇Emax — maximal expiratory flow rate, V̇E50 — expiratory flow rate at 50% vital capacity, FVCI — forced vital capacity on inspiration, V̇Imax — maximal inspiratory flow rate, V̇I50 — inspiratory flow rate at 50% vital capacity.

is important in selecting the optimum treatment method (eg, whether vocal fold lateralization or nerve-muscle pedicle).

Evaluation. The objectives in clinical evaluation are recognition of BVFMI, first; assessment of presence or absence of each of the four vocal cord motion–limiting factors, second; and determination of severity of upper airway obstruction, third. The symmetric appearance of the vocal cords camouflages BVFMI, and distinguishing passive vocal cord mobility from paralysis is often difficult. Hence, examination at direct laryngoscopy should include assessment of passive mobility of the arytenoids and vocal fold tone and stiffness. Contour of the glottic aperture, particularly when tear-shaped; absence of mucosal corrugation in the interarytenoid fold; and a rounded, rather than squared, configuration at the posterior commissure are features that indicate presence of cicatricial bands or webs.

Electromyographic examination is the most certain method for ascertaining neuromuscular integrity. The flow-volume loop spirogram (FVLS) identifies the site, nature, and severity of upper airway obstruction and demonstrates a characteristic pattern of variable extrathoracic obstruction in vocal cord paralysis, unilateral and bilateral.[1] Two distinct FVLS patterns are observed in upper airway obstruction due to BVFMI. When flow rate limitation occurs during both inspiration and expiration, the FVLS pattern is termed fixed; this pattern is observed in cases of VFIL (see Figure, C and Table 2). An FVLS pattern with selective inspiratory flow rate limitation and normal expiratory flow rate is termed variable extrathoracic obstruction (VEO; see Figure; A,B and Table 2). The VEO pattern is observed in BVFP, CAJF, and cicatricial webs. The FVLS examination, serially performed, objectively documents improvement or progression in respiratory flow rates and is an ideal reference standard for determining airway adequacy. A mid-vital capacity flow rate (V̇I50) of 1.5 L/s is the necessary threshold for moderate activity in most adults.

Management. The surgical objective in BVFMI is to expand the inspiratory glottic aperture dimension so as to enhance the inspiratory flow rate and, simultaneously, to reduce the expiratory glottic aperture to minimize excessive airflow on expiration (air wastage) and to achieve effective vocal cord apposition for phonation. To simultaneously increase and decrease glottic dimensions in a nondynamic larynx is impossible; this ideal result is achieved only by restoration of voluntary vocal cord motion. However, direct anastomosis of injured laryngeal nerves has not been successful.[2]

The partial posterior cordectomy by surgical laser enlarges the posterior glottic aperture and preserves close approximation of the anterior membranous vocal cord for phonation.[3] In lieu of cordectomy, a transverse cordotomy, immediately anterior to the vocal process, results in a wedge-shaped widening of the posterior glottis due to retraction of the divided thyroarytenoideus muscle. This triangular defect gradually assumes a rounded tear-shaped opening, and glottic airway enhancement is directly proportional to the extent of vocal cord incision. Contracture of the anterior portion of the divided thyroarytenoideus increases vocal cord mass and favors a midline position for better vocal cord apposition and effective voice production. This transverse cordotomy operation offers the advantages of simplicity, minimal trauma, and a predictable degree of airway enhancement. When additional airway enlargement is necessary, a revision operation with further transverse division of the ipsilateral or contralateral vocal cord is performed. Neither cricoarytenoid joint fixation nor glottic web nor infiltrative disorders and fibrosis of the vocal cords limits effectiveness of this operation to achieve airway improvement.

Dennis and Kashima, who conceived the posterior cordectomy operation, have reported that this operation can be relatively safely performed without preliminary tracheotomy.[3] Virtually all of our patients present with a tracheostomy, which we vent for several weeks postoperatively until the final airway improvement becomes stabilized.

In six cases reported by Dennis and Kashima in their original communication, the $\dot{V}_{I50}$ was improved from 0.89 L/s (0.55 to 2.20) to 1.60 L/s (0.61 to 2.22) postoperatively. The preoperative maximal expiratory flow rate ($\dot{V}_{Emax}$) was improved from 3.32 L/s (1.20 to 5.10) to 5.22 L/s (2.09 to 8.13), and the maximal inspiratory flow rate ($\dot{V}_{Imax}$) was improved from 1.32 L/s (0.80 to 2.20) to 2.35 L/s (1.48 to 2.94). On the basis of clinical observation we regard a $\dot{V}_{I50}$ of 1.5 L/s or more to be the critical threshold for reestablishing a safe and effective airway.

CASE REPORTS

Case 1. A 63-year-old man (see Figure, A) presented with persistent dyspnea and a weakened voice 3 months after a coronary artery bypass operation following which several endotracheal intubations were necessary. At operative endoscopy he had posterior glottic webs and arytenoid fixation, in addition to BVFP. Cordotomy improved his $\dot{V}_{I50}$ from 0.99 L/s to 2.30 L/s, and an improved airway was restored.

Case 2. A 29-year-old man (see Figure, B) sustained a closed head injury in a motor vehicle accident. He was unable to be decannulated after neurologic recovery. A posterior glottic web and unilateral vocal fold paralysis were documented. Cordotomy improved his $\dot{V}_{I50}$ from 1.74 L/s to 2.28 L/s. He was decannulated and has resumed work as a construction worker.

Case 3. A 69-year-old man (see Figure, C) underwent a supraglottic laryngectomy in 1982 and received a course of postoperative irradiation therapy. He developed progressive dyspnea due to BVFMI and required a tracheotomy placement. His vocal cords were densely fibrotic. Cordotomy improved his $\dot{V}_{I50}$ from 1.26 L/s to 2.09 L/s and he was safely decannulated.

DISCUSSION

Tracheotomy with use of a valved tracheotomy tube is a management choice of high reliability and minimal morbidity. It is particularly well suited for individuals with severe comorbidities and airway instability. Voice quality is preserved.

The objective in subtotal cordectomy operations is air passage enlargement by reduction of a vocal cord mass. The final airway caliber is not precisely predictable and the voice result is imperfect. Use of the surgical laser has improved precision of vocal cord excisions, and novel techniques for reduction of vocal cord mass with preservation of mucosa will likely be developed.

The arytenoid cartilage, by virtue of its crucial relationship to the lateral and posterior cricoarytenoid, interarytenoid, and thyroarytenoid muscles, logically has long been the focus of surgical interest to achieve vocal cord lateralization. Although numerous surgical techniques have been described in minute detail, exposure of the arytenoid is difficult and usually suboptimal; the necessary muscle detachments are more readily achieved in textbook diagrams than in the operative field. Moreover, in CAJF with infiltrative or fibrotic lesions of the vocal fold, lateralization of the arytenoids and vocal cords is difficult to achieve, and in the presence of webs, the opposite vocal cord is drawn toward the repositioned arytenoid, minimizing the intended enlargement of the posterior glottic aperture. In spite of these limitations, a high proportion of successful rehabilitation in bilateral vocal fold "paralysis" has been achieved by experienced surgeons.[4] Arytenoid removal alone is not adequate for improving the glottic airway without deliberate scar production laterally, as emphasized by Thornell, who regarded this step to be a critical part of the endoscopic arytenoidectomy operation.[5] Arytenoidopexy is suitable in BVFP without other vocal cord–restraining factors.

Neurotization of the posterior cricoarytenoid to restore vocal cord abduction is a delicate operation that requires an atraumatic surgical technique and minimal scarring. The neuromuscular pedicle operation is unlikely to succeed in cases of long-standing paralysis, but satisfactory results have been achieved in selected cases when it was performed by experienced surgeons.[6] Neurotization would not be expected to be successful in cases with CAJF, VFIL, or cicatricial webs.

CONCLUSION

Although BVFP has been and continues to be a relatively uncommon disorder, BVFMI due to paralysis, CAJF, VFIL, or cicatricial webs is encountered with increasing frequency in the current era of complex medical treatments. This presentation suggests that distinguishing these BVFMI subgroups and recognizing their unique features will lead to improved results in their management.

The patient with BVFMI syndrome is plagued by a precarious airway, often in the presence of one or more serious comorbidities. In such settings, a straightforward and reliable airway restoration is of paramount importance. Transverse cordotomy by carbon dioxide laser appears ideally suited to achieve this goal.

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MANAGEMENT OF CRANIAL BASE DISEASES

A one-day comprehensive review of contemporary management of cranial base diseases for neurosurgeons, otolaryngologists, ophthalmologists, radiation oncologists, and reconstructive surgeons will be held Nov 10, 1991, at the Ritz-Carlton Hotel in San Francisco, California. The course directors are Phillip H. Gutin, MD; Robert K. Jackler, MD; and Lawrence H. Pitts, MD. For further information, contact Extended Programs in Medical Education, Room LS-105, University of California School of Medicine, San Francisco, CA 94143-0742; (415) 476-4251.

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The Casselberry Award has been established to encourage the advancement of the art and science of laryngology and rhinology. The award is given for outstanding theses or accomplishments in laryngology and rhinology, and consists of a suitable sum of money (up to $2,000) and a certificate from the Association. Competition for this award will be limited to those persons whose abstracts are selected for consideration for inclusion in the annual scientific program. Those wishing to compete for this award must submit their entries in the form of a complete manuscript to ALA President John M. Fredrickson, MD, Washington University Medical School, 517 South Euclid Avenue, St Louis, MO 63110, no later than November 29, 1991. The candidates and manuscripts will be reviewed by a committee; if a winner is selected, the Casselberry Award will be presented at the annual scientific meeting.

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ETHMOID SURGERY COMPLICATIONS AND THEIR AVOIDANCE

ALAN SOGG, MD
CLEVELAND, OHIO

BERKLEY EICHEL, MD
TORRANCE, CALIFORNIA

The purpose of this report is to review the complications that two experienced operators have encountered during the past 20 years. The techniques employed by the authors are similar. Three thousand intranasal nonendoscopic procedures accumulated between the coauthors were further evaluated to explain why complications could occur. There were five dural injuries in this series that were managed conservatively. Periorbital ecchymoses were seen in 9% of the cases with no permanent adverse sequelae. Approximately 0.5% of the patients had postoperative bleeding. Conclusions that the authors reached were as follows. 1) A complication as a result of ethmoid sinus surgery can occur with any technique and in the hands of any surgeon. 2) Training and experience plus knowledge of the ethmoid anatomy may help reduce the absolute number of complications. 3) Early recognition of a complication and its appropriate management can help decrease the relative severity of the complication. 4) The surgeon should terminate a procedure when visualization and localization are compromised.

KEY WORDS — complications, ethmoid surgery.

INTRODUCTION

The development of the endoscopically performed ethmoid operation[1] has stimulated renewed interest in this type of surgery. It has also again brought to our attention that ethmoid surgery, regardless of the technique employed, has its potential dangers as currently[2-4] and previously reported,[5,6] in spite of a report to the contrary.[7]

The authors, who trained in different programs at approximately the same time, perform a nonendoscopic modified Yankauer procedure that both have described.[8,9] Their total ethmoid operative experience of 3,000 ethmoidectomies has been combined to examine the types of complications encountered and their severity. The complications are listed and methods for avoiding them discussed.

METHODS

The surgical indications for the patients in this study, from the total clinical experience of the authors, have been covered in previous publications.[8,9]

The authors both employ a modified Yankauer technique in that a portion of the middle turbinate is usually preserved and the dissection is started at the ethmoid bulla, when technically possible, because of its constancy.[10]

The total number of cases and any resulting complications have been combined, since the only major difference in technique between the authors was that one (B.E.) operated with general anesthesia and the other (A.S.) used local standby anesthesia.

The techniques employed for avoiding complication, or minimizing one should it occur, are described in the Discussion.

RESULTS

Minor Complications. Excessive bleeding, ie, that requiring termination of the procedure with resultant subsequent surgery to complete the originally planned operation, occurred in 15 patients or 0.3% of the series. Periorbital ecchymoses occurred in 270 patients or 9%. (These 270 complications occurred during the total operative experience of the authors — more than 20 years each. Our current rate of periorbital ecchymoses is less than 5%.) Two of these 270 patients had temporary (2 to 6 weeks) diplopia. Synechiae occurred in less than 1.0%, as did septal hematoma. Numbness of the upper incisors (temporary) occurred in 50%. This was a result of the injection for and/or creation of a mega-antrostomy in the inferior meatus. Noncompliance of patients in prolonged follow-up created the increased likelihood of recurrent problems. Up to 50% of the patients do not return as frequently or for as many years for follow-up examinations as is suggested.

Major Complications. Cerebrospinal fluid leaks occurred in 5 patients (0.17%), 3 of whom required mucosal or fascial closure. Two of these had pneumoencephaloceles and 1 of these developed meningitis. All recovered without further sequelae. Two of these patients developed their leaks at least 1 year following the operation. Postoperative bleeding requiring hospitalization and packing occurred in 14 patients or 0.47%. Two of these patients required transfusion. Several of these patients had bleeding from the antrostomy opening. While other complications such as permanent diplopia, blindness, and death have been described in the literature or anecdotally, they did not occur in this series and are therefore omitted. The total major complication rate in this series was 0.64%.

DISCUSSION

The number and severity of the complications

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REPRINTS — Alan Sogg, MD, 21100 Southgate Park Blvd, Cleveland, OH 44137.

that were encountered we feel are not unacceptable and compare favorably with those in other reports. While other operative methods have previously been described and specific techniques advocated, the avoidance of complications has not been stressed. We both realize that a description of "avoidance techniques" is anecdotal and are disquieted by the fact that avoidance of complications defies statistical analysis. However, we will proceed, keeping in mind that the art of medicine must survive in the interest of well-rounded teaching and patient safety.

Since the seriousness of a complication varies, we have separated ours, as have others, into minor and major. We therefore have listed periorbital ecchymoses with the possible removal of a small amount of periorbital fat (without further intraorbital damage) as being minor. A dural tear, because of its different implications, is considered a major complication with or without further morbidity. We believe the inclusion of patient noncompliance as a minor complication merits explanation. Patients may not return for appropriate follow-up for several reasons, including their own perception that they are doing well and see no need for further visits to the operating surgeon. Possibly, the need for periodic examinations to help recognize and prevent recurrent problems was not stressed by the surgeon. A patient who requires reoperation will most likely have either distorted anatomy or absent landmarks and as a result be more at risk for a possible surgical complication.

There are, of course, many factors that contribute to the occurrence of complications and, ultimately, why they occur or, more important, do not occur. The depth of one's training and operative experience can be significant, even though it is acknowledged that any surgeon may have a problem. Early recognition of, for example, periorbital fat will likely prevent a serious orbital complication even though the patient will have periorbital ecchymoses. Gentle pressure on suspected periorbital fat intranasally can cause an obvious movement of the eye as seen externally. Conversely, gentle external pressure on the globe may cause movement of the suspected periorbital fat as viewed intranasally. If need be, a frozen section of the suspected fat can remove all doubt. The use of saline to see if the polyp sinks or the fat floats can be helpful. Further prevention of orbital complications is promoted by doing this operation with the patient awake. The sedated patient will generally respond to pain when periorbital fat is pulled with an instrument. This type of response can help alert the surgeon that he or she may be in a potentially dangerous area.

The recognition of one or more of the critical ethmoid landmarks is mandatory in the performance of this surgery. These include the ethmoid bulla, the medial wall of the middle turbinate, the anterior wall of the sphenoid (which can also be found transseptally), the fovea ethmoidalis, the anterior attachment of the middle turbinate to the lateral nasal wall, and a spatial appreciation of one's location in the ethmoid or sphenoid. If the operating surgeon is unsure of their location, one or more of the above-mentioned structures should be defined by either direct visualization or with the aid of a radiograph with appropriate markers. If the surgeon is unsure of their location in spite of all measures (and measurements[11,12]) at his or her disposal, it is the feeling of the authors that the safest course of action would be termination of the operation. This latter statement would apply whenever visualization and exposure are compromised from any cause, such as excessive bleeding or when the amount of blood loss is reaching the level that could possibly require transfusion. Dissection should only be performed under direct vision, regardless of the surgical technique. The operator should constantly keep in mind the relationships of the ethmoid labyrinth, such as the proximity of the posterior lateral ethmoid to the optic nerve. Also, instrumentation performed intranasally above the external inner canthal landmark can be dangerous.

A clear stream of fluid as opposed to blood should be recognized for what it is and managed appropriately. A cerebrospinal fluid leak may occur from dissecting when exposure is insufficient (see above) or from fovea rupture, particularly in areas of relative thinness of the bone.[13]

The prevention of excessive bleeding is aided by use of local anesthesia and injection of vasoconstrictors,[3] which should also be employed with general anesthesia.

CONCLUSIONS

1. A complication as a result of ethmoid sinus surgery can occur with any technique employed and in the hands of any surgeon.
2. Training and experience plus knowledge of the ethmoid anatomy may help reduce the absolute number of complications.
3. Early recognition of a complication and its appropriate management can help decrease the relative severity of the complication.
4. The surgeon should terminate a procedure when visualization and localization are compromised.

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Ann Otol Rhinol Laryngol 100:1991

STROBOVIDEOLARYNGOSCOPY: RESULTS AND CLINICAL VALUE

ROBERT T. SATALOFF, MD

JOSEPH R. SPIEGEL, MD MARY J. HAWKSHAW, RN

PHILADELPHIA, PENNSYLVANIA

Strobovideolaryngoscopy is a valuable addition to the diagnostic armamentarium because it allows the otolaryngologist to perform a detailed physical examination of the vibratory margin of the vocal fold. From 1985 through 1989, we performed 1,876 strobovideolaryngoscopy procedures, the majority on professional voice users. Previously, we reported findings on our first 486 strobovideolaryngoscopy procedures. Stroboscopic information influenced diagnosis or treatment in approximately one third. The present study was undertaken to determine whether additional experience had altered the clinical usefulness of the procedure. Diagnoses were noted before and after stroboscopy prospectively for 377 strobovideolaryngoscopy procedures performed during the calendar year 1989. In 53% of the procedures, strobovideolaryngoscopy resulted in no change in diagnosis. In 29%, preprocedure impressions were confirmed and additional diagnoses were made. In 18%, preprocedure diagnoses were found to be incorrect. The procedure has proven very helpful in caring for voice patients, modifying diagnoses in 47%, and confirming uncertain diagnoses in many of the other patients studied.

KEY WORDS — stroboscopy, strobovideolaryngoscopy, voice.

Complex motion of the vibratory margin of the vocal folds is essential for normal voice. Because the vocal folds open and close between about 60 and 1,500 times per second depending upon the pitch of phonation, valid, reliable physical examination of the vibratory margin cannot be accomplished by using continuous light and a laryngeal mirror. High-speed photography permits slow-motion evaluation of vocal fold vibration, but it is cumbersome. It also permits evaluation of only relatively short samples of phonation. High-speed video is not widely available and shares many disadvantages with high-speed photography. Strobovideolaryngoscopy is currently the most convenient technique permitting the otolaryngologist to perform a detailed assessment of the vibratory margin of the vocal fold. From 1985 through 1989, we performed 1,876 strobovideolaryngoscopy procedures. All strobovideolaryngoscopic examinations were performed by an otolaryngologist, usually with the assistance of a nurse, speech-language pathologist, and/or singing voice specialist. The majority were on professional voice users. Previously, we reported findings on our first 486 strobovideolaryngoscopy procedures.[1] Stroboscopic information influenced diagnosis or treatment in approximately one third of cases. The present study was undertaken to determine whether additional experience had altered the clinical usefulness of the procedure.

MATERIALS AND METHODS

Three hundred seventy-seven strobovideolaryngoscopy procedures were performed on 352 patients between January 1, 1989, and December 31, 1989. During that period, we saw 583 voice patients for a total of 1,180 voice-related visits. The 377 visits during which strobovideolaryngoscopy was performed comprised approximately 32% of voice patient visits, and stroboscopy was performed on 60% of the patients seen during that period. All patients were selected because of the presence or suspicion of a structural or neurologic abnormality, or to prove the absence of such a lesion. Of the 352 patients who underwent strobovideolaryngoscopy, the majority were professional voice users, and 129 of these were singers. The other patients also sought medical attention specifically for voice complaints.

All stroboscopic examinations were performed with a Bruel and Kjaer rhinolarynx stroboscope type 4914, with the patient seated. An Olympus flexible nasolaryngoscope and a magnifying telescope were used in virtually all cases. Initially, examinations were performed while looking directly into the laryngoscope before connecting it to the video system. In some cases, the laryngoscope was also connected to a Zeiss operating microscope using a custom-made adaptor, before strobovideolaryngoscopy. This technique provides high-quality magnification, which is especially helpful in those few patients who will not tolerate the laryngeal telescope. The flexible laryngoscope permits observation of vocal fold function under continuous and stroboscopic light during a variety of phonatory tasks, with relatively undistorted vocal tract anatomy. The magnification and high optical quality provided by a rigid laryngeal telescope are invaluable and obviate the need for magnification with an operating microscope in most cases. However, they permit vocal fold evaluation only during relatively awkward vocal tract positions and tasks. Simultaneous synchronized electroglottography was also performed, and the electroglottographic waveform

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From the Department of Otolaryngology, Thomas Jefferson University (Sataloff, Spiegel), and the American Institute for Voice and Ear Research (Hawkshaw), Philadelphia, Pennsylvania.

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REPRINTS — Robert T. Sataloff, MD, 1721 Pine St, Philadelphia, PA 19103.

TABLE 1. FORTY ENTITIES OBSERVED DURING 377 STROBOVIDEOLARYNGOSCOPIC PROCEDURES

Diagnosis	*No. of Procedures*	*No. of Patients*
Arytenoid dislocation	2	2
Cancer	4	3
Cricothyroid fusion	1	1
Cysts	10	8
Dysarthria	1	1
Dysphonia	50	45
Dysphonia plica ventricularis	8	5
Functional dysphonia	9	9
Foreign body	1	1
Granuloma	3	3
Hemorrhage	30	26
Histoplasmosis	1	1
Hoarseness	2	2
Laryngeal spasm	7	2
Laryngitis	21	18
Leukoplakia	2	1
Lymphoid hyperplasia	2	1
Mass	87	86
Mucosal tear	6	6
Myasthenia gravis	3	3
Nerve paralysis or paresis	66	59
Nodules	34	32
Normal	7	5
Parkinson's disease	1	1
Polyp	6	4
Presbyphonia	12	10
Reflux laryngitis	186	165
Reinke's edema	10	4
Respiratory dysfunction	1	1
Sarcoidosis	1	1
Scar with stiffness	59	32
Subglottic stenosis	1	1
Temporomandibular joint syndrome	1	1
Tonsillitis	1	1
Trauma	4	3
Ulcer	1	1
Upper respiratory tract infection	1	1
Varicosity	11	10
Voice abuse*	133	126
Web	5	5

*Includes hypofunctional and hyperfunctional voice abuse, muscular tension dysphonia, and improper singing or speaking technique.

was superimposed on the laryngeal image. Electroglottography provides an assessment of each vibratory event. This is a valuable adjunct because the stroboscope only simulates slow motion by imaging fragments of successive vibratory cycles. All examinations were recorded on videotape and stored. Duplicates were made routinely for the referring physician, speech-language pathologist, singing teacher, or patient. Black and white and color video printers are also connected to the system for documentation and patient education.

Our videostroboscopy protocol involves speaking at various frequencies and intensities, pitch sliding, sniffing, whistling, rapid repetition of syllables, singing, sustained vowel phonation, and other selected tasks. Observations are recorded about voice quality, laryngeal color, vocal fold motion, vibratory margin motion, structural abnormalities, supraglottic muscle function, and other findings. Symmetry, periodicity, glottic closure, amplitudes, waveforms, and nonvibrating segments are assessed by using a modification of the format proposed by Hirano.[2] In all cases, prior to strobovideolaryngoscopy diagnoses were recorded based on clinical examination using a laryngeal mirror, and examination of the singing voice when appropriate. Diagnoses based on the strobovideolaryngoscopic examination were compared with preprocedure diagnoses to determine whether strobovideolaryngoscopy was helpful clinically in establishing diagnoses or treatment strategies. We were also interested in determining whether additional clinical and teaching experience since the time of our original report in 1988 had altered the usefulness of strobovideolaryngoscopy in our practice.

TABLE 2. NUMBER OF PROCEDURES EXPERIENCED BY INDIVIDUAL PATIENTS

No. of Procedures per Patient	*Patients*	
	No.	*%*
1	326	93
2	23	6.5
3	1	< 1
4	2	< 1

RESULTS

Three hundred seventy-seven strobovideolaryngoscopic examinations were performed on 352 patients. Forty entities were diagnosed (Table 1). Many patients had more than one diagnosis, although some had their second, third, or fourth diagnosis established at separate office visits during the 12-month period. For example, a patient with voice abuse and a varicosity on one visit may have returned with a vocal fold hemorrhage. Table 1 lists each diagnosis every time it was observed during strobovideolaryngoscopy, even if it was present on several examinations in the same patient. Table 1 also lists the number of patients who had each diagnosis at any time during the 12-month period. Seven percent of patients underwent more than one strobovideolaryngoscopic procedure (Table 2). Most of the patients who underwent two or more procedures had vocal fold hemorrhage, vocal nodules, or unrelated problems on different occasions during the 12-month period. In 110 procedures (29%), stroboscopy confirmed the clinical diagnosis and permitted detection of additional diagnoses. In 67 procedures (18%), the clinical diagnosis was found to be incorrect. Thus, during 177 procedures (47%) strobovideolaryngoscopy provided additional diagnostic information. In 55 cases, the additional findings did not alter medical management. The 122 cases (32.4% of procedures) in which clinically significant findings were detected only following strobovideolaryngoscopy are summarized in Table 3. These examples include cases of small recurrent carcinoma, cases of delayed resolution of vocal fold hemorrhage, cases of recurrent laryngeal nerve pa-

TABLE 3. CASES IN WHICH STROBOSCOPY MADE SIGNIFICANT DIFFERENCE IN DIAGNOSIS AND/OR TREATMENT

Lesion	*No. of Procedures*
Carcinoma	1
Cricothyroid fusion	2
Cyst	7
Cyst and contact nodule	4
Granuloma	2
Hemorrhage	10
Mass	12
Mucosal tear	5
Myasthenia gravis	2
Nodules	8
Normal larynx with functional dysphonia	3
Polyp	2
Recurrent laryngeal nerve paresis	10
Scar	32
Superior laryngeal nerve paresis or paralysis	16
Varicosity	3
Web	3

resis initially thought to have been paralysis, cases in which vocal fold scar was detected unexpectedly in the presence of other vocal fold disorders such as nodules or cysts, and other conditions. Stroboscopy allowed diagnosis of vocal fold cysts with contralateral reactive nodules in several cases that had been misdiagnosed as bilateral vocal nodules. Accurate stroboscopic diagnosis in these cases altered the treatment plan and decreased the amount of time spent in voice therapy prior to surgical intervention. Stroboscopy is also helpful in documenting normal vocal fold function in cases of psychogenic dysphonia or malingering. Malingering is increasingly common as the number of lawsuits following surgical procedures continues to increase.

DISCUSSION

Use of stroboscopic light to evaluate the larynx was first reported in 1895.[3] Since that time, more than 90 articles have recommended the technique, and numerous equipment designs have been proposed, as cited previously.[1] Recent improvements in laryngeal stroboscopes have provided instrumentation that is practical for clinical use. The technique has proven helpful in evaluating many patients with voice complaints, providing rapid assessment of vibratory function. This permits diagnosis of structural lesions that are often missed altogether without stroboscopy. In comparing our current findings with those reported in our 1988 study, we were somewhat surprised to note a 12% increase in the percentage of voice visits during which stroboscopy was performed. We believe this is due not to expanded indications for stroboscopy, but rather to the increasing percentage of our patients referred by otolaryngologists for complex medical or legal consultation. In our previous investigation, we reported that stroboscopy provided clinically valuable information in 31.2% of the procedures performed. In our present study, there were additional findings in 47% of procedures, but important diagnostic changes in only 32.4%. These remarkably consistent findings confirm the conclusions put forth in our previous report. Strobovideolaryngoscopy provides valuable information that alters diagnosis and/or treatment in about one third of patients for whom the procedure is indicated. It is helpful in confirming clinical impressions in many additional patients. Once skill has been acquired in performing and interpreting strobovideolaryngoscopy, extensive experience does not appear to alter its clinical value. Stroboscopic findings routinely result in changes in diagnosis that alter treatment strategies. We have found the technique invaluable in daily practice and essential for valid, reliable diagnosis of voice disorders.

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SPECIAL INSTRUMENTS FOR LARYNGEAL FRAMEWORK SURGERY

NOBUHIKO ISSHIKI, MD
HISAYOSHI KOJIMA, MD MASAKI SAWADA, MD
KYOTO, JAPAN

Thyroplasties involve a variety of delicate surgical techniques that affect the outcome decisively. In particular, opening a window in the thyroid cartilage, undermining around the window frame and fixation of a window plug in thyroplasty, and passing a suture through the muscular process and thyroid ala are some examples of difficult procedures. Several instruments were devised to facilitate such procedures. They include a special raspatory, an ultrasonic osteotome for cartilage cutting, a narrow polyvinyl tube for suture passing, a suture holder for passing through the muscular process, and a wound retractor for arytenoid adduction. These were found useful in minimizing soft tissue damage and in precise performance of the procedures.

KEY WORDS — instruments, laryngeal framework surgery, thyroplasty, ultrasonic osteotome.

The voice result after laryngeal framework surgery largely depends on how it was performed, especially in terms of design and expertise of each surgical step. In thyroplasty type I, for instance, a rectangular window must be made at the right place on the thyroid ala with minimal damage inside the inner perichondrium so that intraoperative adjustment to the voice will be accurate. Several instruments have been found useful for this purpose.

INSTRUMENTS FOR THYROPLASTY TYPE I

Ultrasonic Osteotome. Fenestration in the thyroid ala is usually done with a B-P No. 11 blade in women and with a fine bur in older men whose thyroid cartilage is calcified. In order to avoid inadvertent cutting of the inner perichondrium, the last deep, thin layer of the cartilage is often cracked gently with a hemostatic chisel rather than cut with a knife.

A new instrument has recently been developed to cut hard material only, avoiding any damage to soft tissue underneath such as blood vessels. It is the ultrasonic osteotome (Sumisonic ME-2400, Sumitomo Bakelite Co, Ltd).

Figure 1 schematically shows a horn tip of the instrument that vibrates to and fro at an ultrasonic frequency with an amplitude of 200 μm. A water shower from the back of the blade automatically cools the heat resulting from friction. The soft tissue underneath is not cut, because it is easily distorted in accordance with the vibration, as illustrated. Be-

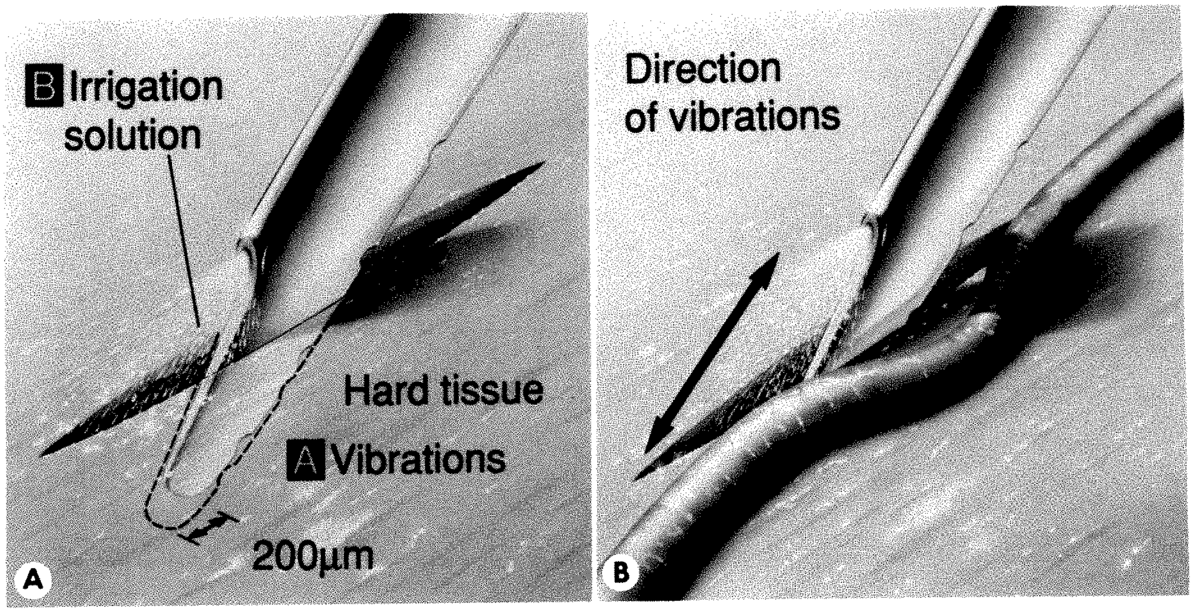

Fig 1. Schematic illustration of ultrasonic osteotome. A) Tip of instrument vibrates at ultrasonic frequency, cutting hard material only. Shower is provided from horn to cool friction heat. B) Soft tissue underneath will not be cut.

From the Departments of Plastic Surgery (Isshiki, Sawada) and Otorhinolaryngology (Kojima), Kyoto University, Kyoto, Japan.

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REPRINTS — Nobuhiko Isshiki, MD, Dept of Plastic Surgery, Medical School, Kyoto University, Sakyo-ku, Kyoto 606, Japan.

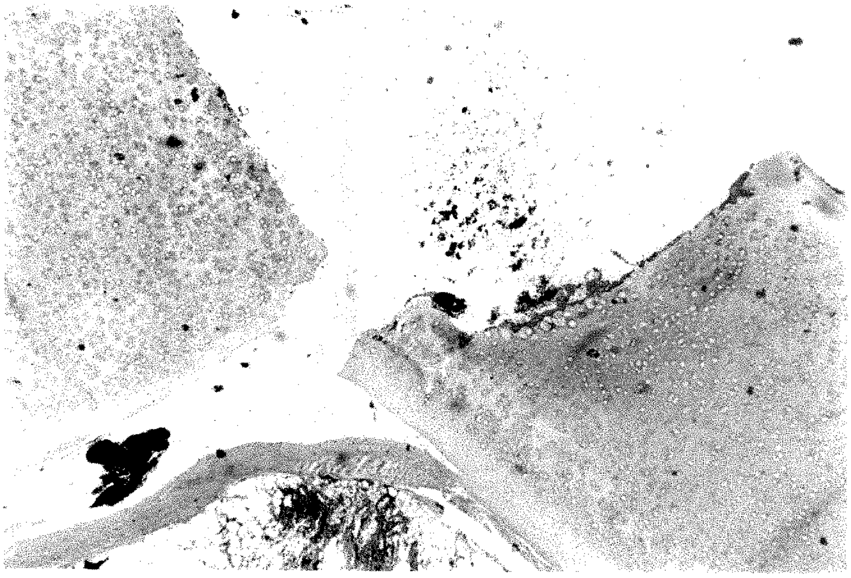

Fig 2. Histologic findings in incised rabbit rib cartilage and intact underlying soft tissue.

fore clinical application, a series of experiments were conducted in the rabbit to assess the extent of damage to the soft tissue under the rib cartilage. Histologic examinations of the composite hard and soft tissue to which the ultrasonic osteotome was applied all revealed intact soft tissue (Fig 2). This finding has led us to use it in laryngofissure and thyroplasty. During the procedure of cutting through the cartilage, not a drop of bleeding was noted. There is no doubt of the intended effect. The disadvantages would be its price and the water shower required to cool the heat accumulation.

Because it is expensive, we only borrowed it for a while for a pilot study. The high-pressure shower may accelerate the development of local edema.

Fixation of Window. Medialization of the vocal cord is adjusted during thyroplasty type I by trying plugs of various thicknesses. A thickness-adjustable silicone plug was produced (Fig 3A). It can be

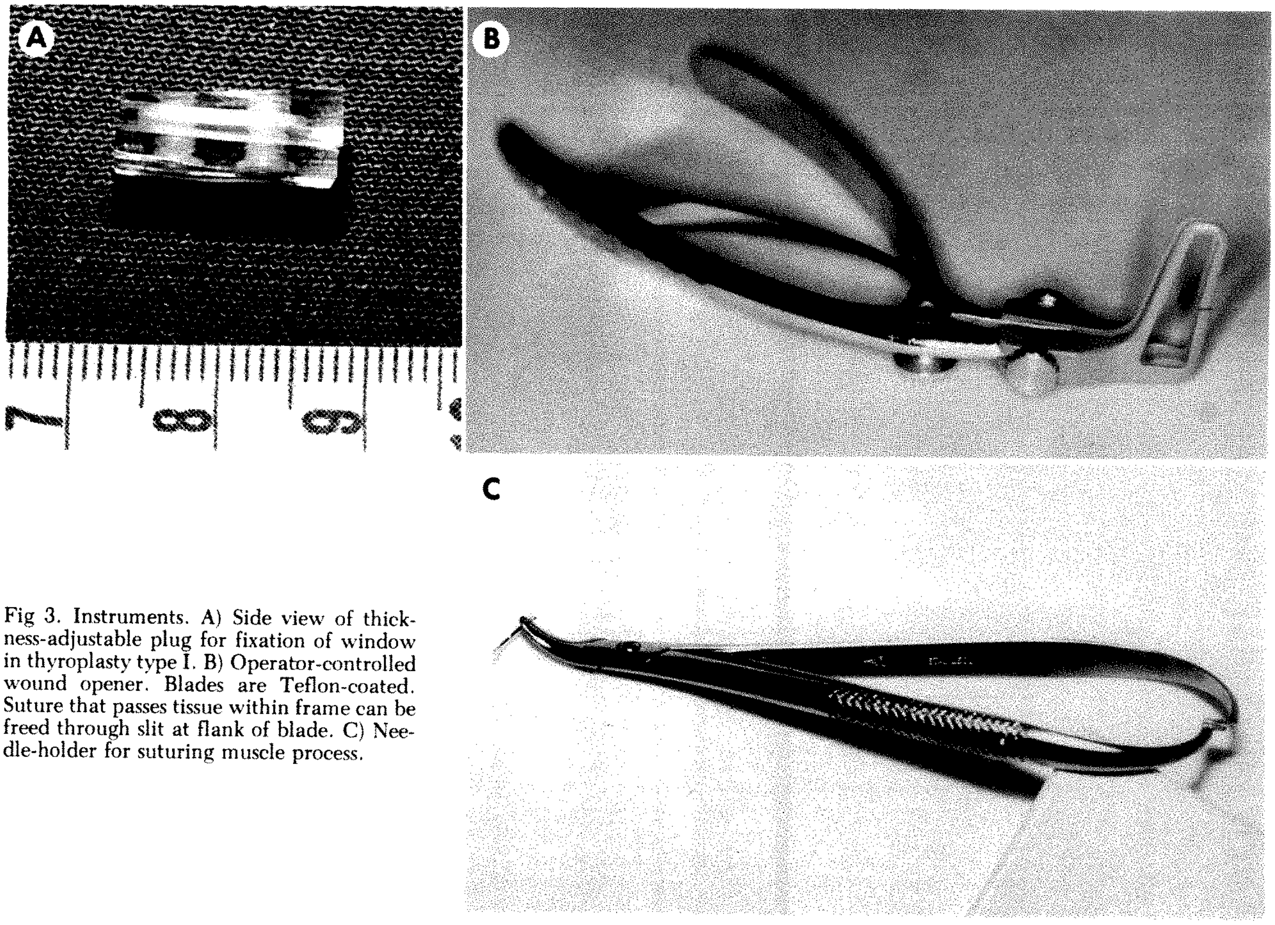

Fig 3. Instruments. A) Side view of thickness-adjustable plug for fixation of window in thyroplasty type I. B) Operator-controlled wound opener. Blades are Teflon-coated. Suture that passes tissue within frame can be freed through slit at flank of blade. C) Needle-holder for suturing muscle process.

screwed down to produce fine adjustments in thickness during surgery. It may be useful also for adjustment of medialization in a second operation, which may become necessary because of later atrophy or subsidence of edema of the vocal cord after the initial operation.

ARYTENOID ADDUCTION

Arytenoid adduction is generally more effective in medializing the vocal cord than thyroplasty type I. Difficulty in arytenoid adduction technique may be in 1) access to the muscular process, 2) suturing the process, or 3) adjustment of adduction to the voice.

The former two problems can be eased considerably by using a special wound opener and a needle holder. The wound opener is basically a type of nasal speculum that is controlled by one hand of the surgeon (Fig 3B). It is modified, however, in two ways: the blades take the shape of a frame with a narrow opening so that one can obtain better vision and can pass the needle for suturing through the tissue that is squeezed from within the frame. A narrow opening at the flank of the frame is necessary when the passed suture is freed from the opener. The frame blades are silicone-coated to enable relatively safe electrocoagulation by means of a metal suction tube inserted between the opener blades.

Passing a needle through the muscular process within a deep and narrow surgical field is another procedure that is difficult to perform. A needle holder with a curved tip was found to be helpful (Fig 3C).

Several instruments are reported that facilitate surgical procedures in laryngeal framework surgery. Some are practical and others still need further modification.

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HEAD AND NECK SURVEILLANCE PROGRAM FOR FACTORY PERSONNEL EXPOSED TO ASBESTOS

STEVEN M. PARNES, MD MALCOLM SHERMAN, PHD

ALBANY, NEW YORK

Personnel at a local factory that manufactures brake linings and discs in which asbestos is a major component were requested to participate in an on-site surveillance program to detect head and neck abnormalities, specifically cancer. Demographic data included smoking histories and job descriptions that could be delineated into high- and low-asbestos exposure groups. In the first year, 322 factory workers had no cancer identified but 15% had laryngeal abnormalities, mostly laryngitis. Ninety-seven percent of those workers with abnormal findings were smokers, but there were a significant number in the high-asbestos group irrespective of smoking histories. From this report, high-risk individuals were identified and requested to continue in the program for monitoring. In the subsequent 3 years, these individuals and new personnel were examined. Similar results were obtained in that laryngitis was noted in 24% (95% of whom were smokers) with a stronger statistical association with the high-asbestos group. More important, one person previously identified as high-risk was noted to have stage I squamous cell carcinoma and was treated with radiotherapy. The results of this program suggest that individuals at high risk for the development of head and neck cancer can be identified and that such surveillance programs should be implemented in similar arenas.

KEY WORDS — asbestos, head and neck cancer, surveillance programs.

INTRODUCTION

Exposure to asbestos evokes a morbid fear of cancer and permanent disability. There has been an explosive growth of asbestos identification and removal companies as a result of the mandate by the Environmental Protection Agency and the Asbestos Hazard Emergency Response Act. To comply with these regulations will cost industry and the public approximately $53 billion and perhaps as high as $100 to $150 billion.[1] Despite these policies, the exact risk of disease from this exposure remains unclear.

It has been well established that in workers having direct contact with asbestos, there is an increased occurrence of diseases, particularly cancer of the lung, mesothelioma, and asbestosis.[2-8] The relationship of cancer of the larynx to asbestos exposure remains extremely controversial. There have been a number of studies on this subject with extensive review of data from the literature. In evaluating the same data bases and cohort studies, the authors have reported conflicting results and interpretations.[9-16] This is due in part to the fact that cancer of the larynx has a relatively small fatality rate in contrast to lung cancer; thus, the large-cohort mortality studies do not provide a satisfactory way of investigating this entity. The advantage is, however, that the types of fibers and degree of exposure in terms of duration are known. Unfortunately, smoking and drinking habits have often been omitted. As an alternative, the case control studies have been more attractive, since they focus on laryngeal cancer. However, they also suffer from potential difficulties, since precise exposure histories are lacking and there is the investigators' potential bias to the patient population they are evaluating. The type of asbestos can be critical, since a preponderance of evidence seems to point to the increased risks and hazards associated with the amphibole type of asbestos as compared to the far more prevalent chrysotile type.

There have been a few studies[16-18] in which the investigators used cross-sectional methods to examine the individuals at risk from asbestos exposure. Two studies[16,18] performed on-site head and neck examinations to determine the effects of asbestos on the head and neck areas. Both reported similar findings. The workers with high asbestos exposure had significantly increased findings of alterations in the laryngeal mucosa, but in neither case was carcinoma of the larynx identified.

This investigation and a previous one[16] were motivated by the discovery of three cases of cancer of the larynx over a period of 10 years among the employees in a single plant that uses asbestos. Initially, a large number of personnel were noted to have laryngeal disease, mostly laryngitis, which had a significant association with exposure to asbestos. This study represents a 3-year follow-up with continued monitoring of individuals who were initially considered at high risk. It further evaluates the relationship between exposure to asbestos and laryngitis.

METHOD

A head and neck surveillance program was de-

From the Division of Otolaryngology–Head and Neck Surgery, The Albany Medical College (Parnes), and the Department of Biometry and Statistics–School of Public Health, State University of New York at Albany (Sherman), Albany, New York. Supported by a grant from Allied Chemical, Inc.

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REPRINTS — Steven M. Parnes, MD, Division of Otolaryngology–Head and Neck Surgery, A-41, The Albany Medical College, 47 New Scotland Ave, Albany, NY 12208.

signed and implemented for a local factory that manufactures brake linings and discs in which chrysotile asbestos is a major component. Data were obtained from the safety personnel regarding various levels of asbestos at different locations. In addition, information from safety reports regarding other potential contaminants was obtained. Occupations were categorized as low-risk (less than 0.1 fiber per cubic centimeter) and high-risk (greater than or equal to 0.1 fiber per cubic centimeter). These categories were dependent upon location within the building as well as peculiarities of the individual occupation. In general, low-risk exposure included all office workers, executives, and professional employees who had minimal contact with the asbestos and are comparable to the normal population. All other personnel (those who worked in the building in which asbestos was prevalent) were identified as the high-risk group. Initially, the program was made available to all personnel on a volunteer basis. The senior author approached the factory workers through formal presentations to indicate the purpose and logistics of the program, particularly in reference to early detection of cancer of the head and the larynx. Of the approximately 500 employees, 322 (65%) agreed to the examination and signed formal consent forms to participate in the study. Each individual had a complete head and neck examination, including the nose, oral cavity, oropharynx, nasal pharynx, larynx, and neck, performed by the senior author (90%) or other otolaryngologists. Just prior to each examination, the individual filled out a questionnaire designed to elicit the following symptoms: hemoptysis, dysphagia, loss of weight, neck mass, cough, and hoarseness. Also obtained were smoking and alcohol histories, occupation, date of birth, sex, race, and length of employment. Any positive responses were discussed during the head and neck examination. This information was tabulated and incorporated into a data base on a personal computer and has been previously reported.[16] Through analysis of the original data, high-risk groups were identified. These included all subjects with positive findings and alterations of laryngeal mucosa as well as those who were smokers. These individuals were then requested to participate in continued monitoring in the subsequent 2 years. New personnel were also permitted to participate. These results were also tabulated and then analyzed independently and in combination with the original reported series.

STATISTICAL ANALYSIS

Observed incidence of laryngitis or other laryngeal disease was related to asbestos exposure, allowing for the effects of smoking and checking on the relevance of other potential explanatory factors, including alcohol use, age, race, sex, and employment years. Data were analyzed with SAS software on a mainframe computer.

The potential relationship between probability of laryngitis and asbestos was investigated by means of a standard logit model to relate probability p of laryngitis, and a quantified measure of smoking, asbestos exposure, and some other factors, including age and years of working at the plant. Logit (p) is defined as the natural logarithm of the odds ratio (p/1 − p), which is assumed to be a linear function of other variables. Thus, one model investigated is

$$\text{Logit (p)} = \log p/1-p = A + B \text{ x smoking index} + C \text{ x asbestos level} \qquad (1)$$

If the fitted values of B and C are positive and if the probability that the true values are zero or negative can be ruled out statistically, then the model states that as smoking increases, so does the incidence of laryngitis and there is a greater probability of laryngitis at asbestos level 1 (high exposure) than at level zero (low exposure). Since the subjects studied were selected precisely because of presumed elevated risk, the overall incidence of laryngitis should be higher than it would be for all workers at this type of plant. Even though the value of the constant A is presumably greater than for a sample of all workers in the plant, the constants B and C should still indicate the magnitude of the effect of smoking and the magnitude of the effect, if any, associated with asbestos exposure.

A variable, smoking index (Smkindex), is used as a measure of smoking risk in the present study. It is defined in terms of two other variables, lifetime pack-years (PY) and years elapsed since smoking was given up (NS). Thus, if a subject smoked 1.5 packs per day for 20 years but gave up smoking 5 years before the examination, the value of PY would be 30 = 20 x 1.5 and NS = 5. Smoking index (Smkindex) is defined as PY times an attenuation factor that reduces risk for persons who gave up smoking. The actual formula is

$$\text{Smkindex} = \text{PY} \exp[-2\,\text{NS}/(\text{PY} + 2\text{NS})] \qquad (2)$$

($\text{Exp}[a] = e^a$, where e = 2.71828 is the base of natural logarithms.) Thus, in the example, Smkindex = 30 exp[−10/(30 + 10)] = 30 x 0.779 = 23.4. For someone who smoked briefly and gave up smoking long ago, the attenuation factor will be not much more than about $e^{-1} = 0.368$, so that such a person has the same risk factor as a present smoker who had smoked only about 40% as much. The attenuation factor is, of course, equal to 1 for current smokers. For nonsmokers, Smkindex is equal to zero. For those who smoke cigars or a pipe but not cigarettes, PY is defined as one tenth the product of the number of years of smoking times either the number of cigars per day or the number of times per day the pipe is smoked.

RESULTS

There were 212 employees who participated in

TABLE 1. PERSONNEL

Asbestos Exposure	*No. of Cases*	*Smokers*	*Laryngitis*	*% With Laryngitis Who Smoked*
High	144	122	43	98
Low	96	48	14	86
Total	240	170	57	95

TABLE 2. PHYSICAL EXAMINATION RESULTS

	No. of Cases	*% of Patients*
Normal	123	51.0
Deviated nasal septum	60	25.0
Laryngitis	57	24.0
Neck node or mass	5	2.1
Carcinoma of larynx	1	0.4
Other	16	6.6

the follow-up examination, 63 of whom had been examined previously, and 28 were subsequently seen twice. One hundred seventy-five examinations took place between November 1987 and February 1988, while the remaining 65 were conducted in January and February 1990. The participants ranged in age from 22 to 66 (average, 43), with 210 men and 170 smokers (66 had quit). As noted in Table 1, 43 of the 144 employees in the high-exposure group had laryngitis, of whom 98% smoked. In the low-asbestos exposure group (96), there were 14 patients who had laryngitis, of whom 86% smoked.

Normal examination results were noted in 123 employees (51%) (Table 2). There were 139 abnormalities noted, of which the most common was deviated nasal septum (60 cases or 25%), followed by laryngitis defined by either erythema or edema (57 cases or 24%), one of which proved to be a squamous cell carcinoma. Three employees required some type of operative intervention. One was a direct laryngoscopy and biopsy and, as noted, the lesion proved to be a stage I squamous cell carcinoma of the larynx. This patient received full-course irradiation and remains disease-free after 1 year. The second had a neck node biopsy that showed the node to be benign and the third had removal of a lesion of the oral cavity, pathologically demonstrating a papilloma.

The incidence of laryngitis was then analyzed in reference to the low- and high-asbestos groups with smoking accounted for (Table 3). At both levels, the number of cases of laryngitis increased with smoking, although the effect is much clearer at the higher-asbestos level. Smoking exposure is defined as none for nonsmokers, low for those in whom the Smkindex is between 0 and 15, medium for those from whom the Smkindex is between 15 and 35, and high for those from whom the Smkindex is above 35. The statistical analysis was based on 212 employees, using data for the second visit on the 28 that were examined twice. The Smkindex was found to have a higher correlation with laryngitis than did PY.

If the logit curves for the low- and high-asbestos groups are parallel, fitted values for the model give the following formula.

$$\text{Logit (p)} = -2.4105 + 0.90304 \text{ x (asbestos)} + 0.03281 \text{ x (Smkindex)} \tag{3}$$

The coefficient of Smkindex is highly significant (p = .0018). Similarly, the coefficient of asbestos was significant, with a p value of .024. The fact that the coefficient of asbestos groups is not zero means that there are differences in probability of laryngitis that are associated with asbestos level (and not, for example, with any tendency for the group with greater asbestos exposure to smoke more). These estimates have a high substantial margin of sampling error, and it is probably not likely that the curves behave in a parallel manner, but rather that the high- and low-asbestos populations do differ significantly with respect to asbestos, even taking smoking into account. The model then is determined separately for each group. The formula for the low group would be

$$\text{Logit (p)} = -2.2333 + .02168 \text{ x (Smkindex)} \tag{4}$$

The formula for the high group would be

$$\text{Logit (p)} = -1.6047 + .03829 \text{ x (Smkindex)} \tag{5}$$

In the low-asbestos group, the coefficient of Smkindex is not statistically different from zero (p = .247). Among the high group the coefficient is highly significant (p = .0034) (Fig 1). According to this model, a nonsmoker in the low group has an odds ratio for laryngitis of 0.110, which corresponds to a probability of .099, while a nonsmoker in the high group has an odds ratio of 0.187 and a probability of .158. Thus, in this model asbestos is associated with higher risk — a risk difference that increases with increasing levels of smoking and probably invalidates the assumption that the logits were parallel (ie, that the difference in logs of odds ratio was independent from smoking).

TABLE 3. INCIDENCE OF LARYNGITIS BY ASBESTOS EXPOSURE AND SMOKING

Asbestos Level	*Smoke Exposure*	*Normal*	*Laryngitis*	*Total*
Low	None	42	2	44
	Low	11	2	13
	Medium	11	5	16
	High	9	2	11
	Total	73	11	84
High	None	19	1	20
	Low	44	12	56
	Medium	24	17	41
	High	6	5	11
	Total	93	35	128
Total	None	61	3	64
	Low	55	14	69
	Medium	35	22	57
	High	15	7	22
	Total	166	46	212

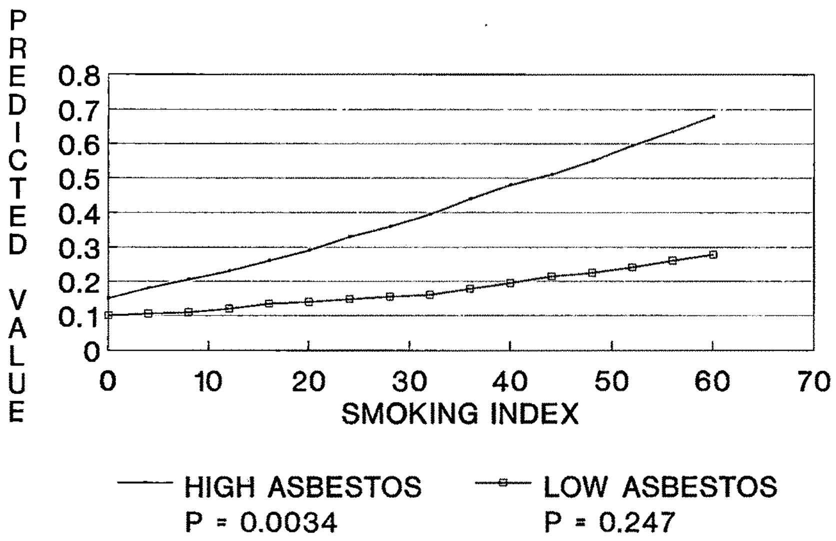

Fig 1. Probability of laryngitis at two asbestos levels (new data).

A similar pattern emerges from combining this data base with that from the previously reported study.[16] A total of 467 individuals were examined, with a total of 562 encounters. A tabulation of the incidence of laryngitis, asbestos exposure, and smoking appears in Table 4. There was an overall incidence of laryngitis of 19 of 240 in the low-asbestos group and 43 of 227 in the high-asbestos group. The fitted values for this model gave the following formula for the low group.

$$\text{Logit (p)} = -2.7289 + .01868 \text{ x } (\text{Smkindex}) \quad (6)$$

In the high-exposure group the formula was

$$\text{Logit (p)} = -2.2303 + .040837 \text{ x } (\text{Smkindex}) \quad (7)$$

The coefficient for Smkindex is not statistically different from zero in the low group ($p = .130$), while it is highly significant ($p = .0001$) in the high group (Fig 2). Thus, there exists a significant positive association of asbestos level with laryngitis, accounting for relatively large changes in the observed incidence of laryngitis.

One other interesting finding was the difference in laryngitis between men and women. Of the 29 women most recently examined, 15 were in the low-asbestos group and 14 in the high-asbestos group. Only 1 had laryngitis, while 25% of the men had laryngitis. While the women were a bit younger and somewhat less likely to smoke, these differences were not large enough to explain a disparity of this magnitude. The single woman with laryngitis smoked an average of one pack a day for the previous 7 years and did work in the high-exposure group for less than 1 year. While the sample sizes for women were too small to give reliable correlations, the evidence as a whole suggests the possibility that associations between asbestos and laryngitis may differ for men and women.

DISCUSSION

Asbestos is a broad commercial term for a group of naturally occurring hydrated silicates that crystallize into a fibrous form. The family of asbestos minerals can be subdivided into serpentine and amphibole fibers. Chrysotile, a serpentine type, is the most common asbestos fiber, accounting for 90% of the world's production, whereas the amphibole is a diverse group of less industrially important minerals including crocidolite, amosite, anthophyllite, actinolite, and tremolite asbestos.[15] In this factory in which this head and neck surveillance occurred, chrysotile was the only type of asbestos used. There are other chemicals in the plant, but according to the safety personnel, these were all within safety standards set by the Occupational Safety and Health Administration. It is extremely important to distinguish among the different types of asbestos, since mortality appears to be highest among those workers who work with amphibole alone, lower for those who work with mixtures, and lower still among those who work with chrysotile alone.[15,19,20]

One factory worker, a heavy smoker, was found to have a stage I carcinoma of the larynx. No con-

TABLE 4. INCIDENCE OF LARYNGITIS BY ASBESTOS EXPOSURE AND SMOKING (COMBINED DATA)

Asbestos Level	*Smoke Exposure*	*Normal*	*Laryngitis*	*Total*
Low	None	84	3	87
	Low	64	4	68
	Medium	47	9	56
	High	26	3	29
	Total	221	19	240
High	None	43	1	44
	Low	70	12	82
	Medium	49	21	70
	High	22	9	31
	Total	184	43	227
Total	None	127	4	131
	Low	134	16	150
	Medium	96	30	126
	High	48	12	60
	Total	405	62	467

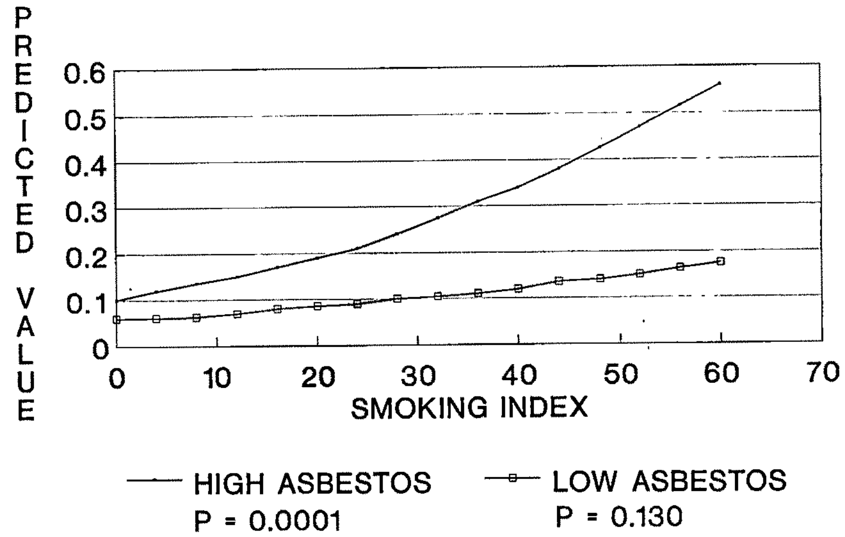

Fig 2. Probability of laryngitis at two asbestos levels (combined data).

clusions can be inferred from this one case. In one study,[21] human laryngeal carcinoma cells were exposed to small chrysotile asbestos fibers. These fibers did penetrate the cell's cytosome and were translocated in proximity to the nucleus. They could also be found inside the nucleus of the interface cells. Findings suggested that after fiber penetration, a rearrangement of the cytoskeletal apparatus did occur and thus can play a role in asbestos intercytoplasmic translocation in epithelial cells. The data also suggested an interaction occurring between the asbestos fibers in the normal mitotic process. Perhaps the disturbance of the cell cytoskeleton causing morphologic contact between asbestos fibers and the cell's nuclear region was important in explaining the carcinogenic effects of the asbestos mineral fibers.

This report also demonstrates that of the employees in this factory, personnel in the high-asbestos group had a significant increase in laryngitis. This statistically significant, positive association, however, is weaker than that demonstrated between smoking and laryngitis. Even if asbestos is a cause of laryngitis, it would appear to be a weak cause among nonsmokers. Several years ago, substantial reductions in asbestos level were achieved in the plant, so that even if past asbestos levels are a factor in the present incidence of laryngitis, it does not follow that further reductions in asbestos would reduce the future incidence of laryngitis. It should be emphasized that if asbestos exposure is a contributing cause of laryngitis, it does not follow that asbestos is a cause of cancer of the larynx. A statistical association does not prove the existence of a causal relationship. The present investigation is an observational study, which means that observed associations may be due to uncontrollable confounding factors. To effectively eliminate this possibility would require that subjects be randomly assigned to work in high- or low-asbestos areas, which in this case would not be feasible. In addition, the observed statistical relationship noted may well result from confounding of asbestos exposure with other sociologic or physical factors. High-exposure jobs are factory jobs, while most of the low-exposure jobs are office jobs. There could well be off-the-job behavioral differences among these occupational groups that are related to laryngitis. For example, it is possible that factory workers drink more hard liquor and beer than office workers. Alcohol use has been found in numerous studies to act as a throat irritant. In the earlier study,[16] workers were asked about alcohol consumption, but self-reported alcohol usage did not appear to be related to the incidence of laryngitis. However, it seems most likely that workers would be hesitant to report large, off-the-job alcohol consumption to an examining doctor whose investigation is sponsored by the employer. Although the literature suggests that alcohol should be a cause of laryngitis and of other throat irritations, a failure to detect a relationship between alcohol and laryngitis is probably due to the tendency of workers to deny or minimize their drinking.

There could be differences in work air quality that are unrelated to asbestos that account for the differences in laryngitis between factory workers and office workers. While air quality at the plant is now quite good, even the cleanest factory is presumably dustier than an office. There might also be differences in ambient noise levels between factory jobs and office jobs so that factory workers are more likely to strain their voices in conversation. Such differences might contribute to the observed incidence of laryngitis among factory workers.

The noted difference between sexes is difficult to explain. The asbestos may be confounded with other causes, or perhaps one can speculate on the possible causes of such sex disparity. For example, alcohol consumption could be an important factor, since men tend to drink more than women. There may also be other socioeconomic differences between the men and women. The women at the plant are more likely to have an employed spouse and therefore may have a higher family income.

Thus, it appears that the asbestos fibers may have some effect on laryngeal mucosa, as demonstrated clinically and experimentally.[21] While there was one laryngeal carcinoma detected in our population, this was in a patient who was a heavy smoker, and smoking is a well-known established risk factor for laryngeal cancer.[22-26] The review articles examining epidemiologic studies on this subject[9,12-16,27] have divergent conclusions. Although it is not proven that asbestos exposure leads to cancer of the larynx, one must be concerned that it may act as a cofactor in individuals already at high risk, ie, smokers.

The surveillance program in this plant has proven successful, then, in identifying high-risk individuals, particularly the employee with stage I carcinoma. It also served to educate the personnel concerning the dangers of smoking. This program is ongoing and will serve as a model for other plants that use similar raw materials.

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MAGNETIC RESONANCE IMAGING OF PEDIATRIC HEAD AND NECK CYSTIC HYGROMAS

WILLIAM T. C. YUH, MD, MSEE
IOWA CITY, IOWA

LINDA S. BUEHNER, MD
IOWA CITY, IOWA

SIMON C. S. KAO, MD
IOWA CITY, IOWA

ROBERT A. ROBINSON, MD, PHD
IOWA CITY, IOWA

KENNETH D. DOLAN, MD
IOWA CITY, IOWA

JEFFREY J. PHILLIPS, MD
TORRANCE, CALIFORNIA

We retrospectively reviewed the magnetic resonance imaging (MRI) findings of eight pathologically proved cystic hygromas in seven pediatric patients. All lesions showed multiple cysts, best depicted on T2-weighted images (T2WI). Six of the eight lesions had well-defined borders. Fluid-fluid levels were visualized in seven of eight lesions, with very high signal intensity of the upper fluid on T2WI. On T1-weighted images, all lesions showed a mean signal intensity greater than that of muscle (1.6 times) and cerebrospinal fluid (CSF; 4.04 times) and less than that of fat (0.5 times). On T2WI, the mean signal intensity was greater than that of CSF (1.8 times), muscle (9.45 times), and fat (2.54 times). Chemical analysis of the cystic fluid from one lesion showed high lipid content and hemorrhage, consistent with the preoperative and in vitro MRI findings on the fluid from the same patient. Lesion anatomic distribution showed frequent posterior triangle involvement; however, the epicenter of 75% of the lesions was outside the posterior triangle. Only one lesion had involvement limited to the posterior triangle. There was equal distribution of right and left sides and no midline lesion. Seven lesions displaced the sternocleidomastoid muscle laterally, whereas one displaced it posteriorly, with no evidence of muscle infiltration. Only those patients with submucosal involvement (two of seven) had respiratory symptoms. Gadolinium provided no additional information with regard to diagnosis or extent of involvement. Our experience indicates that MRI is useful in the diagnosis and treatment planning of cystic hygromas.

KEY WORDS — cystic hygroma, magnetic resonance imaging.

Cystic hygromas are developmental tumors of lymphatic origin, most common in the neck region. Radiologic findings of these lesions by plain film, sonography, and computed tomography (CT) have been well established.[1-3] Recently, Siegel et al[4] reported magnetic resonance imaging (MRI) findings of lymphangiomas in children. We retrospectively studied the MRI characteristics of cystic hygroma, a subset of lymphangiomas, with specific attention to anatomic distribution and both quantitative and qualitative analyses.

MATERIALS AND METHODS

We retrospectively reviewed the MRI findings of eight pathologically proved cystic hygromas in seven pediatric patients. There were three boys and four girls, ranging in age from 1 week to 5½ years (mean age, 25 months). One patient had two lesions. Two patients also had postoperative follow-up with MRI. Cystic contents were chemically analyzed and imaged in vitro by MRI in only one patient. All MRI examinations were performed with either a 0.5-T (Picker International, Highland Heights, Ohio) or 1.5-T (GE, Milwaukee, Wis) superconductive unit. At least one T1-weighted image (T1WI) (TR 300-600, TE 20-26) and one T2-weighted image (T2WI) (TR 2,000-2,350, TE 80-100) were obtained in the same plane. Images were also obtained in at least two orthogonal planes. The slice thickness ranged from 0.3 to 1.0 cm (10% to 50% slice gap in the 1.5-T unit). Gadopentetate dimeglumine (Gd-DTPA)-enhanced MRI studies were performed in two patients. Informed parental consent required by our institutional review board was obtained before the intravenous injection of Gd-DTPA (0.1 mmol/kg). Images were obtained immediately after contrast administration by using the same parameters as those of the precontrast T1WI.

Three radiologists reviewed the lesions with attention to signal intensity, fluid-fluid levels, anatomic distribution, definition of margins, contrast enhancement, and postoperative follow-up. Signal intensities were determined by direct measurement from the console of each patient (reload patient's storage tape into the computer) at various areas of interest including upper and lower fluid within various cysts of all lesions. To minimize the variation of signal intensity at various locations, the signal measurements of the other normal structures including fat, muscle, and cerebrospinal fluid (CSF) were chosen at locations nearest to the lesion. The ratios of signal intensity between the cystic content and subcutaneous fat, muscle, and CSF were tabulated in both T1WI and T2WI pulse sequences. The extent of involvement in various anatomic compartments of the lesion was recorded.

RESULTS

All lesions showed multiple cysts (Figs 1 and 2) that were much better depicted by T2WI than T1WI. Septa or walls between two adjacent cysts were shown in all lesions and were best depicted by T2WI. Six of eight lesions showed well-defined bor-

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From the Departments of Radiology (Yuh, Buehner, Kao, Dolan) and Pathology (Robinson), The University of Iowa College of Medicine, Iowa City, Iowa, and the Department of Radiology, Harbor–UCLA Medical Center, Torrance, California (Phillips).

REPRINTS — William T. C. Yuh, MD, MSEE, Dept of Radiology, The University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242.

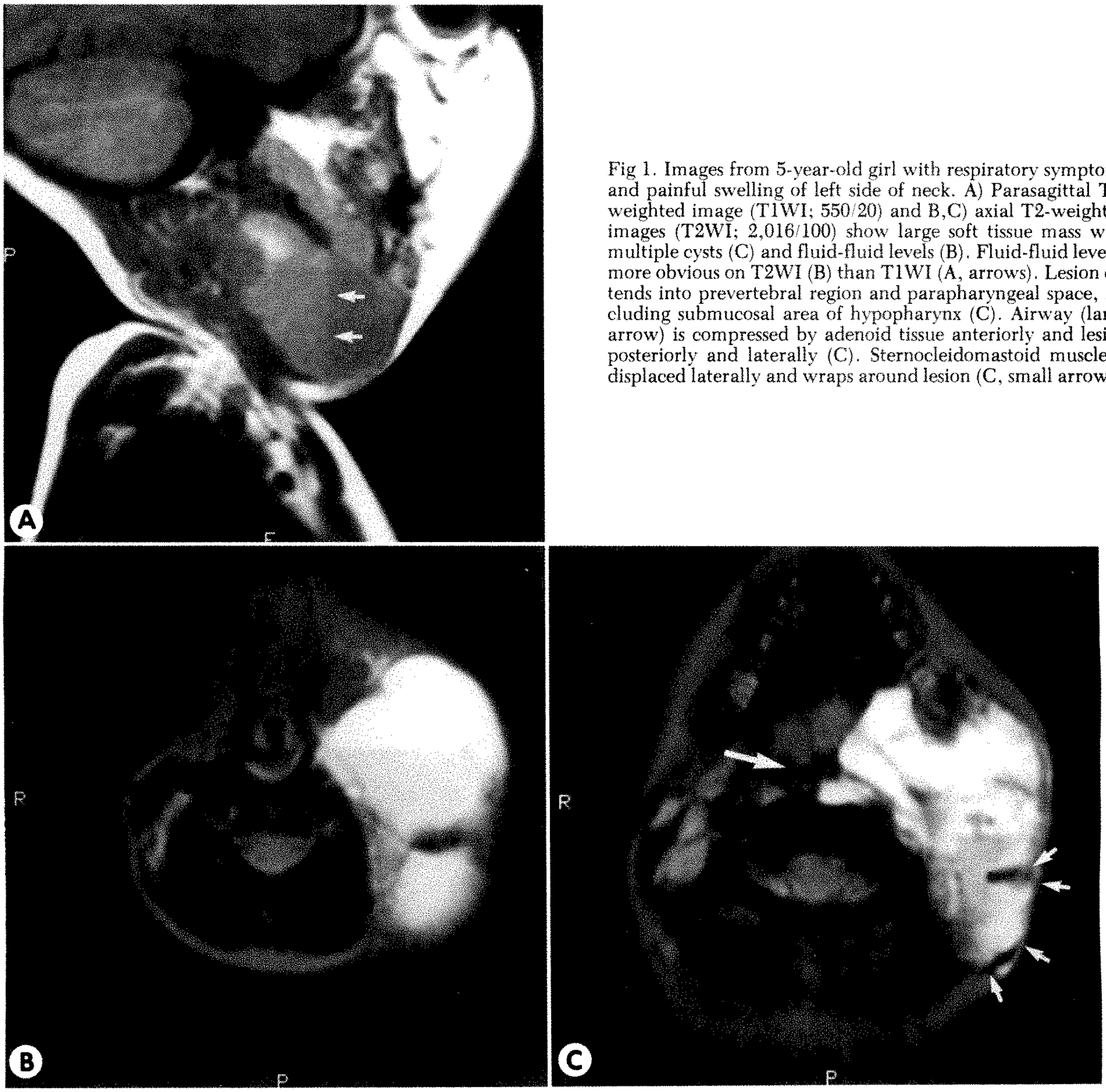

Fig 1. Images from 5-year-old girl with respiratory symptoms and painful swelling of left side of neck. A) Parasagittal T1-weighted image (T1WI; 550/20) and B,C) axial T2-weighted images (T2WI; 2,016/100) show large soft tissue mass with multiple cysts (C) and fluid-fluid levels (B). Fluid-fluid level is more obvious on T2WI (B) than T1WI (A, arrows). Lesion extends into prevertebral region and parapharyngeal space, including submucosal area of hypopharynx (C). Airway (large arrow) is compressed by adenoid tissue anteriorly and lesion posteriorly and laterally (C). Sternocleidomastoid muscle is displaced laterally and wraps around lesion (C, small arrows).

ders, whereas the other two lesions showed ill-defined borders. All lesions were located within the fascia without apparent evidence of muscle infiltration. In seven of eight lesions, the sternocleidomastoid (SCM) muscle was displaced laterally, tending to wrap around the lesions. One patient had posterior and lateral displacement of the SCM muscle (Fig 1C).

Fluid-fluid levels within the cysts were visualized in seven of eight lesions. The one lesion without a demonstrable fluid-fluid level consisted of numerous small cysts. The upper-level fluid usually had a much higher signal intensity on both T1WI (87.5% of all cysts) and T2WI (100% of all cysts) as compared with the lower-level fluid. In vitro MRI examination (1.5-T GE) of the fluid specimen from only one patient (Fig 3) showed similar findings with high signal intensity of the upper-level fluid on both T1WI and T2WI compared with that of the in vivo study (Fig 2). Chemical analysis of this upper-level fluid showed high lipid content (cholesterol 550, normal 120 to 220; triglycerides 229, normal 10 to 180) and methemoglobin from subacute bleeding. In vitro MRI findings of the lower layer showed lower signal intensity on both T1WI and T2WI. Chemical analysis of this lower-level fluid revealed fresh intact blood cells and debris, which accounted for the low signal intensity (deoxyhemoglobin), especially on the T2WI (Fig 3B). Although lipid content was demonstrated in the upper-level fluid, no solid adipose tissue was identified within the lesion in the pathologic specimen or by MRI of all lesions.

Signal intensity of cysts within a lesion usually showed a range of variation among various cysts and between fluid-fluid levels of each cyst. On T1WI, all lesions showed an average signal intensity greater than that of muscle and CSF and less than that of fat (Table 1). The overall average signal of

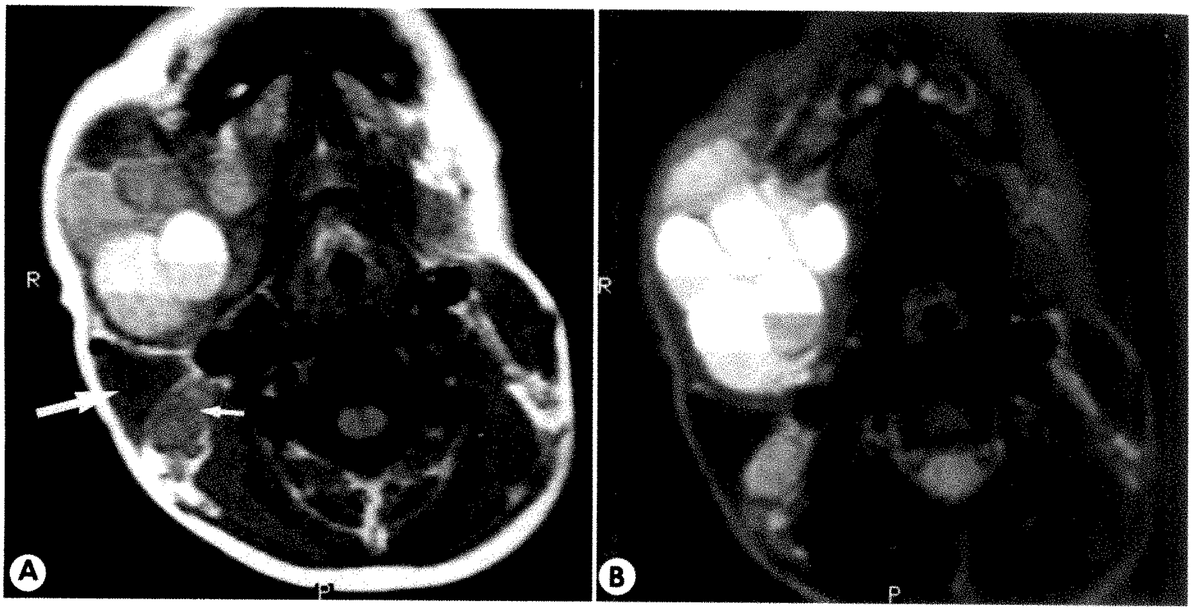

Fig 2. Images from 24-month-old boy with acute progressive swelling of neck without chills or fever. A) Axial T1-weighted image (T1WI; 583/20) and B) T2-weighted image (T2WI; 2,000/100) show multicystic mass with fluid-fluid levels. Upper-level fluid has much higher signal intensity than does lower-level fluid on both T1WI and T2WI. Sternocleidomastoid muscle (large arrow) is displaced posteriorly and laterally between mass and enlarged lymph nodes (small arrow). Note relatively lower signal intensity without fluid-fluid level of lymph nodes on T2WI.

all cysts from all lesions was greater than that of muscle (1.6 times) and much greater than that of CSF (4.04 times) but only half that of fat (0.5 times). On T2WI, the overall average signal intensity of all cysts from all lesions showed a signal ratio greater than that of CSF (1.8), muscle (9.45), and fat (2.54; Table 2).

Lesion anatomic distribution in the cervical region showed frequent posterior triangle involvement in our series. However, only one lesion had involvement limited to the posterior triangle. Seventy-five percent of our cases showed predominant involvement (the epicenter of the mass) outside the posterior triangle. Two lesions showed involvement of the superior mediastinum, one of which recurred postoperatively and was proved surgically. Two patients presenting with signs of airway obstruction had involvement of the submucosal space adjacent to airway and prevertebral spaces (Fig 1C). Lesions were equally distributed to the right and left sides of the neck in our series.

Contrast MRI showed enhancement of the solid portion (cyst walls or septa) of the lesion with clearer definition of the capsule and septa than on non-

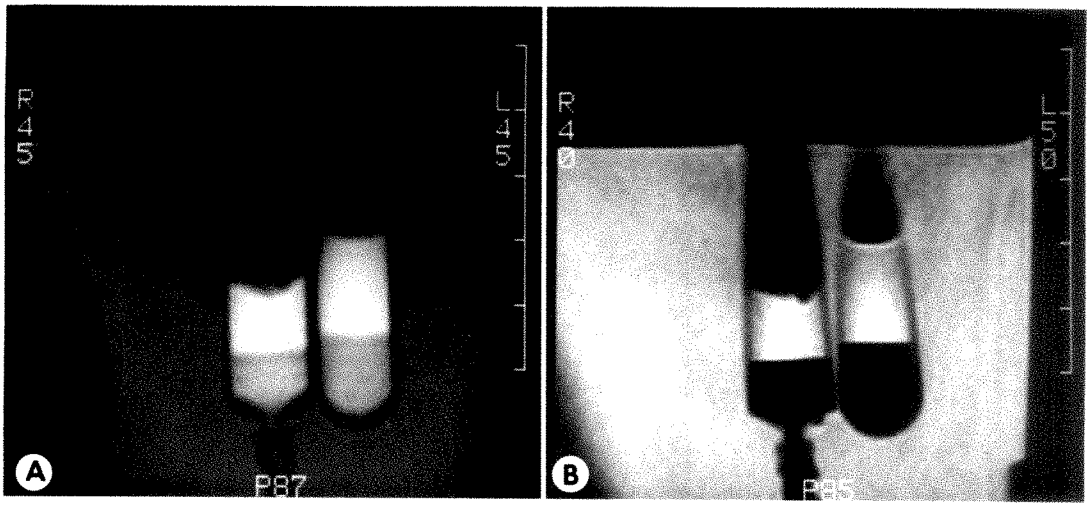

Fig 3. Surgical aspiration of cyst fluid from lesion in Fig 2 was collected in two tubes, both within water container. A) T1-weighted image (T1WI; 600/20) and B) T2-weighted image (T2WI; 2,000/90) show upper-level fluid has higher signal intensity. Chemical analysis of upper-level fluid showed high lipid content (cholesterol and triglycerides). Signal of lower fluid is lower than that of upper fluid on both T1WI and T2WI. These magnetic resonance imaging findings are consistent with laboratory results of intact red blood cells (deoxyhemoglobin) and cell debris.

TABLE 1. T1 SIGNAL RATIO

	Lesion/CSF		*Lesion/Muscle*		*Lesion/Fat*	
Lesion	*Range*	*Mean*	*Range*	*Mean*	*Range*	*Mean*
1	3.3-5.2	4.75	1.4-2.2	1.8	0.5-0.8	0.65
2	2.2-4.0	3.1	0.9-1.7	1.4	0.3-0.5	0.4
3	1.5-2.7	2.1	0.8-1.5	1.15	0.3-0.5	0.4
4	1.9-3.0	2.45	1.0-1.6	1.3	0.4-0.6	0.5
5	5.0-8.0	6.5	1.1-1.8	1.45	0.4-0.6	0.5
6	3.3-4.4	3.85	1.3-1.8	1.65	0.4-0.5	0.45
7	4.0-6.4	5.2	1.5-2.4	1.95	0.5-0.8	0.65
8	3.8-6.0	4.7	1.6-2.6	2.1	0.5-0.8	0.65
Average		4.04		1.6		0.52

CSF — cerebrospinal fluid.

contrast T1WI and T2WI. However, no additional information was provided with regard to diagnosis or extent of involvement in those two patients who received the contrast agent.

Postoperative examinations were obtained in two patients, and MRI findings were consistent with residual tumor in one patient and complete resection in the other.

DISCUSSION

Generally, cystic hygromas, a cystic subtype of lymphangiomas, are considered rare lesions,[5-8] accounting for 5% to 6% of benign tumors and 0.7% to 4.5% of mediastinal tumors of infants and children. Most lesions are seen in younger age groups: 65% to 75% are diagnosed during the first year of life and 80% to 90% by the second to third year. There appears to be a small increase again after the age of 20 years, occurring even into the fifth and sixth decades.[6,9] The male to female incidence rate appears to be equal in most reports, except in the groin area, in which the male incidence is five times greater.[6]

The cervical region is the most common site for cystic hygromas, with a predilection for the left posterior triangle region.[6] This finding correlates well anatomically, because the lymphatic system is more complex and extensive in the cervical region as compared with other areas of the body. Interestingly, our limited number of cases showed equal distribution on both sides. Cystic hygromas derive from the lymphatic tissue in areas in which expansion can occur, and large multiloculated cystic spaces can therefore develop. Our lesions were located predominantly in the fascia planes between the muscles. Most of our lesions expanded anteriorly with the epicenter outside the posterior triangle. Twenty percent occur in the axilla and 5% in other locations such as the mediastinum, retroperitoneum, pelvis, groin, liver, and spleen.[4,6,8]

The most frequent sign of cystic hygroma is the presence of a mass that typically feels like a lipoma or fluid-filled cyst.[6] Difficulties with breathing and swallowing are usually the second and third most common symptoms, caused by lesions extending into the floor of the mouth and tongue, displacing the soft tissues posteriorly into the oropharynx. Small cysts may also occur internally in and around the larynx and hypopharynx, resulting in airway obstruction.[6] In our series, only the two patients with submucosal involvement of the airway had respiratory symptoms (Fig 1C). Therefore, identification of submucosal lesions may be essential in the management of the patient.

On sonography, cystic hygromas show multilocular, predominantly cystic masses with linear septa of various thicknesses, depending on the amount of connective tissue, muscle, and fat between the cysts.[1] All have some solid components related to the cyst walls or septa. Some have echogenic material representing focal hemorrhage or calcification. Sonography is useful in the evaluation of superficial lesions, but not for those lesions involving deep structures.

The CT findings of cystic hygroma include thin-walled, nonenhancing cystic masses filled with near-water density material.[2,3] The cyst wall may enhance with intravenous contrast material. Isodense areas have been described with hemorrhage or infection. Computed tomography more clearly defines anatomic location than plain film or sonography. Bony artifact from the skull base, vertebrae, and shoulder and the isodensity of some cysts may prevent accurate evaluation by CT of the extent of involvement.

Similar to previous reports,[4] our study showed cystic hygroma had signal intensity greater than or equal to that of muscle on T1WI and greater than that of fat on T2WI. All cysts also had signal higher than that of CSF on both T1WI and T2WI, suggesting cyst fluid is very proteinaceous and may contain subacute blood or lipid components. The fluid-fluid level reported by Siegel et al[4] was seen in our cases. However, we also found that the upper-level fluid frequently had a higher signal than did lower-level fluid on T1WI (87.5%) and always had a higher signal than did lower-level fluid on T2WI. Chemical analysis of the upper-level fluid in only one patient showed lower–molecular weight lipid content (cholesterol and triglycerides) consistent with the in

TABLE 2. T2 SIGNAL RATIO

	Lesion/CSF		*Lesion/Muscle*		*Lesion/Fat*	
Lesion	*Range*	*Mean*	*Range*	*Mean*	*Range*	*Mean*
1	2.1-3.0	2.55	7.0-10.0	8.5	2.6-3.7	3.15
2	1.4-1.7	1.55	7.0-9.0	8.0	1.7-2.1	1.9
3	1.0-1.3	1.15	10.0-13.0	11.5	2.0-2.6	2.3
4	1.2-1.4	1.3	12.0-14.0	13.0	2.4-2.8	2.6
5	1.7-3.2	2.45	5.7-10.0	7.85	1.9-3.6	2.75
6	1.6-2.4	2.0	8.0-12.0	10.0	2.0-3.0	2.5
7	1.5-2.7	2.1	5.0-9.0	7.0	1.9-3.4	2.15
8	1.5-2.5	2.0	7.5-12.5	10.0	1.9-3.1	2.5
Average		1.8		9.45		2.54

CSF — cerebrospinal fluid.

vitro MRI of these fluids. In addition, methemoglobin due to subacute bleeding in the upper cyst fluid can also show similar MRI findings. The surrounding fatty septa in those lesions containing smaller cysts with signal equal to that of fat on T1WI reported by Siegel et al[4] were not demonstrable in any of our cases by pathologic examination or MRI. The reason for this is unknown, and it may suggest a subtype of lymphangioma other than the pure cystic hygroma.

Previous reports of spontaneous regression warrant close observation in selected asymptomatic cases.[6,10] Magnetic resonance imaging may play an important role in providing a noninvasive way to follow this group of patients, especially those whose lesions are deep in location. Preoperative MRI demonstrating the exact extent of involvement and the relationship to vital structures, such as mediastinal involvement, is important for surgical planning for complete resection and reduction of recurrences. Because of the characteristic extremely high signal intensity of most cysts as compared with that of the surrounding fat and muscle on T2WI, multiplanar ability, and lack of bony artifact, MRI is an excellent method to outline the extent of involvement. From our limited experience, coronal T2WI is the best image to outline the craniocaudal extension, whereas axial T2WI best defines the involvement of various compartments. Both axial T2WI and coronal T2WI are essential for preoperative planning. Septation is best demonstrated by both T2WI and contrast MRI.

The radiologic differential diagnosis includes hemangioma, lipoma, and other congenital cysts such as branchial cleft cyst and thyroglossal duct cyst.[6,9,11] Hemangiomas typically show serpiginous high signal intensity rather than multiple dilated cystic structures with fluid-fluid level on T2WI.[12] Hemangiomas frequently infiltrate muscle and contain adipose tissue. None of our cases showed typical adipose tissue within the lesion on either T1WI or T2WI. All of our lesions showed displacement rather than infiltration of muscle. Both untreated thyroglossal duct cysts and branchial cleft cysts tend to be unilocular. In addition, branchial cleft cysts may have a much thicker cyst wall. Neither lesion may exhibit fluid-fluid levels with higher signal in the upper-level fluid on T2WI. Branchial cleft cysts are found anterolateral to the carotid sheath and may cause posterior medial displacement of the SCM muscle. Most cystic hygromas arise from the posterior triangle and therefore tend to displace laterally and wrap around the SCM muscle, as seen in seven of our eight cases. Although cystic hygromas may occur in the anterior compartment, involving the submandibular area, this is not a typical location for branchial cleft cysts. Thyroglossal duct cysts typically are located anteriorly in the midline, embedded in the strap muscles. None of our lesions occurred in this location. Lipoma is probably the most difficult to differentiate clinically and the most common misdiagnosis made by the primary physician.[6] However, lipoma has characteristic MRI findings and therefore is easily differentiated from cystic hygroma.

In conclusion, although cystic hygroma has characteristic findings on sonography and CT, both modalities have some limitations. Recognizing the MRI signal and anatomic characteristics of cystic hygroma may be essential to diagnosis. These include multiple cysts with relatively well-demarcated margins and extremely high signal on T2WI, wide range of cyst signal on both T1WI and T2WI, fluid-fluid levels with higher signal in the upper layer, displacement rather than infiltration of muscle, lateral displacement and wrapping around of the SCM muscle, and absence of adipose tissue. Magnetic resonance imaging is also useful (especially the coronal image) in preoperative evaluation of extent of involvement for complete resection and/or conservative evaluation for follow-up of lesions. Submucosal involvement in those patients with airway symptoms can be readily demonstrated. Finally, similar to the contrast agent in CT, Gd-DTPA demonstrated the cyst capsule and septa but offered no information other than that obtained in the noncontrast study.

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HUMAN FETAL UPPER RESPIRATORY TRACT FUNCTION AS REVEALED BY ULTRASONOGRAPHY

GLENN ISAACSON, MD
PHILADELPHIA, PENNSYLVANIA

JASON C. BIRNHOLZ, MD
OAK BROOK, ILLINOIS

The respiratory functions of the oropharynx, larynx, and trachea of normal human fetuses in utero were explored by means of real-time, two-dimensional ultrasonography combined with color-flow and spectral Doppler analysis. Coronal and transverse images revealed the maturation of coordinated respiratory activity of these structures in the late second and early third trimesters. Observation of the effects of these movements upon the flow of amniotic fluid in the fetal respiratory tract provides an appreciation of the early role of the upper airway in the modulation of fetal breathing.

KEY WORDS — Doppler, fetal anatomy, fetus, larynx, respiratory physiology, ultrasound.

INTRODUCTION

In the last century, Preyer[1] speculated that the fetus breathes in utero when he felt rhythmic movements through the maternal abdominal wall. Some 65 years afterward, as cited by Dawes,[2] experiments upon chronically instrumented fetal sheep confirmed antenatal activity of respiratory muscles and measured tracheal fluid flow. Evidence of human fetal breathing movements was reported soon after the development of practical prenatal ultrasound.[3] In fact, diaphragm and chest wall motions are so commonly seen by modern ultrasonography that their presence is used as an indicator of fetal well-being.[4]

Do these movements actually cause an exchange of pulmonary or amniotic fluid, and if so, how is it regulated? One study combining unidimensional Doppler and real-time ultrasonography suggested that flow detected in the fetal neck might represent a pulmonary fluid exchange.[5] Yet, despite such studies of the lower airway, the participation of the upper airway in human fetal breathing remains unknown.

We report the first application of two-dimensional Doppler ultrasound imaging to study directly the anatomy and dynamics of respiratory function in the larynx, pharynx, and trachea of the unborn human.

METHODS

The upper airways of 10 fetuses referred for routine clinical ultrasound examination were studied in utero. All were normal structurally (at birth) and each had gestational age established from known date of conception and by comparing several biometric parameters with standard nomograms. Cases of maternal hypertension, diabetes, and cigarette, drug, or alcohol use were excluded. All studies were performed midmorning, with the mother supine, head and trunk elevated slightly.

Ultrasound imaging was performed with a commercial, large-aperture, dynamically focused system (Acuson, Mountain View, Calif), operating in magnification and low power modes with linear scan format. Frequency was selected (between 3.5 and 7 MHz) depending on tracheal depth from the maternal skin surface. Imaging and Doppler sampling are integrated in this system and share the same transducer array.

The trachea, pharynx, and larynx were surveyed in serial coronal and transverse planes. A specific area within the image could be selected and a range gate maneuvered around it on the ultrasound screen. In this way, the flow within that area of anatomy could be studied and displayed as superimposed color on the black and white image (color-flow Doppler). Red represented flow in one direction, and blue, flow the opposite way. Similarly, a specific area of the image could be studied over time, and the rate of flow within that area expressed on a time-versus-velocity graph (spectral Doppler).

Multiple 7-second periods of pharyngeal and laryngeal motion were captured as 128 sequential images at 60-millisecond intervals and analyzed in slow motion or frame by frame. Color-flow Doppler information was superimposed on each image to determine the relationship of airway configuration to flow.

RESULTS

Breathing. Diaphragm movements were observed in all the second- and third-trimester fetuses during a limited sampling period. Spectral Doppler imaging of fluid flow in the trachea confirmed that these movements indeed prompt a fluid exchange with the amniotic fluid, similar to air movement in postnatal respiration.

From the Department of Pediatric Otolaryngology, St Christopher's Hospital for Children, Philadelphia, Pennsylvania (Isaacson).

Presented at the meeting of the American Society of Pediatric Otolaryngology, Toronto, Canada, May 18, 1990.

REPRINTS — Glenn Isaacson, MD, Dept of Pediatric Otolaryngology, St Christopher's Hospital for Children, Erie Ave at Front St, Philadelphia, PA 19134-1095.

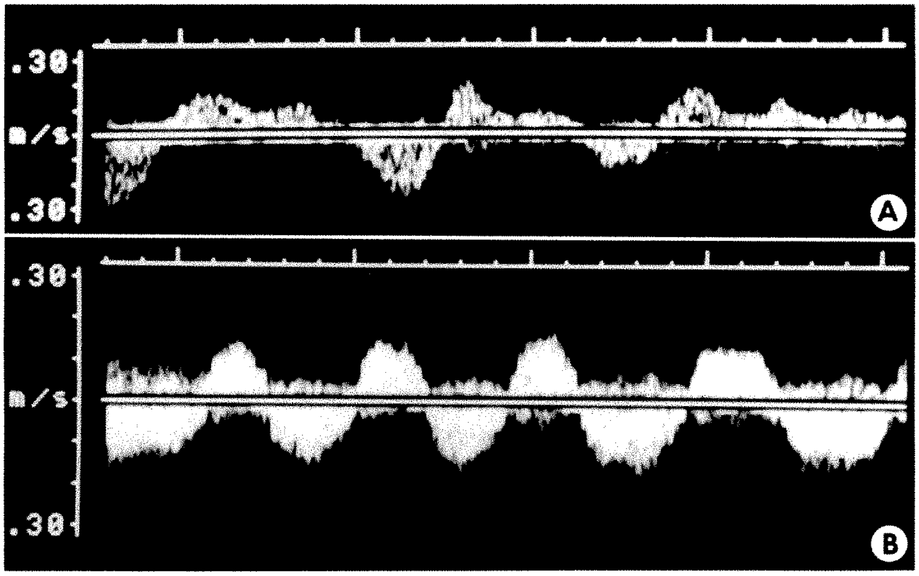

Fig 1. Spectral Doppler ultrasound of tracheal fluid flow as time (1 second = large hash mark) versus flow (meters per second). A) Irregular breathing cycles are typical of younger fetus. B) Regular breathing cycles of third-trimester fetus. Note similar inspiratory and expiratory times.

In the younger fetuses, inspiratory and expiratory flows were often irregular, with marked variation in duration and flow rate (Fig 1A). By the beginning of the third trimester, there was improvement in the regularity of inspiratory and expiratory cycles (Fig 1B). When regular, the rate tended to average 60 breaths per minute, although breath-to-breath variation was evident. The durations of inspiration and expiration were similar in the more mature fetuses.

Pharyngeal Movement. The structure of the pharynx was well seen in transverse and coronal views (Fig 2). The oropharynx was identified as a fluid-filled region within the upper neck, midway between the cervical vertebrae and the anterior skin, and it contained an identifiable epiglottis. Rhythmic expansions of the entire oropharynx were observed 200 milliseconds prior to the onset of inspiration and 100 milliseconds before glottic opening. The pharyngeal lumen narrowed prior to the start of expiratory flow. Pharyngeal dilation consisted of both ventral movement of the tongue base and a prominent outward displacement of the lateral pharyngeal walls.

Laryngeal Movement. Movements of supraglottic, glottic, and subglottic structures were evident on transverse and coronal sections. Abrupt opening of the glottis preceded the onset of inspiratory flow by approximately 100 milliseconds (Fig 3A,B). The true vocal cords, aryepiglottic folds, and conus elasticus moved in unison. While the vocal cords snapped open in a single computer frame, there was a more gradual expansion of the aryepiglottic folds and outward displacement of the conus elasticus in the subglottic region. Relaxation of these structures and return of the cords to a more approximated position preceded the onset of expiration (Fig 4A,B). This position was maintained throughout expiration. The relaxed cords protruded into the expiratory flow stream and resulted in supraglottic turbulence (Fig 4C,D). Little turbulence was evident in the tracheal and subglottic regions during inspiratory or expiratory phases.

Upward displacement of the larynx, probably

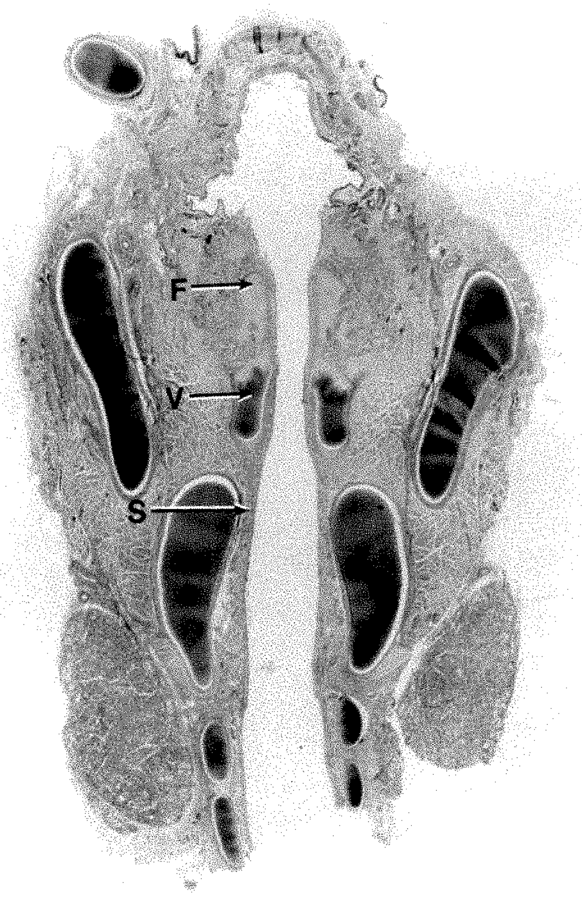

Fig 2. Coronal section of infant larynx. F — aryepiglottic fold, V — vocal process of arytenoid cartilage, S — conus elasticus.

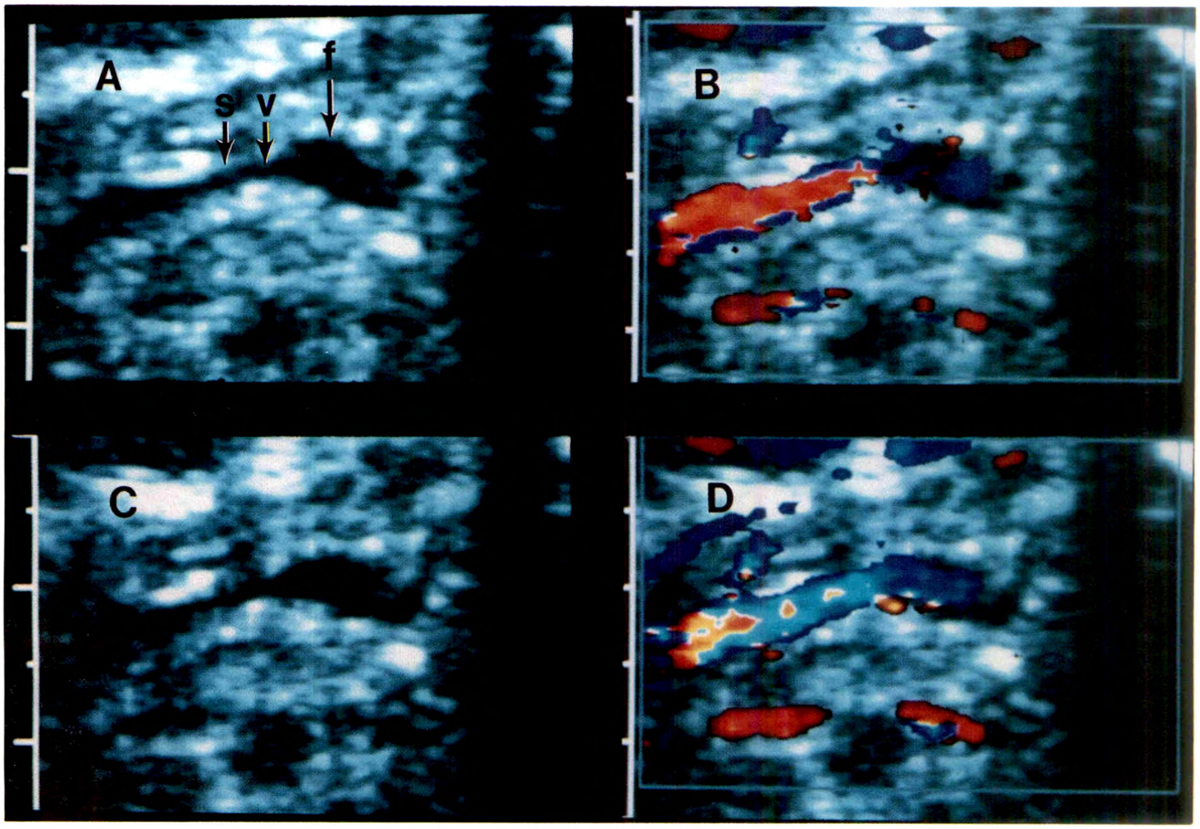

Fig 3. Coronal ultrasound images of fetal larynx in utero. A) Glottis is open in preparation for inspiration. f — aryepiglottic fold, v — glottis, s — subglottis. B) Same as A with Doppler ultrasound. Expiratory flow (red) is just stopping. C) One hundred milliseconds after A. Glottis is open as inspiration begins. D) Same as C with Doppler ultrasound. Inspiratory flow (blue) is evident.

representing fetal swallowing, was noted. Detailed evaluation of laryngeal activity during these excursions was not possible, as the larynx moved too rapidly to pursue with the ultrasound transducer. No evidence of phonatory activity was documented.

DISCUSSION

Fetal breathing is a vital part of prenatal development. Respiratory movements have been demonstrated as early as 11 weeks of gestation by ultrasonography.[4] The incidence and periodicity of respiratory movements progress with gestational age, forming a maturation sequence that parallels other facets of fetal neurologic development.[6,7] Hypercapnia, acidemia, and acoustic stimulation increase incidence and rate of breathing movements in experimental animals, and severe hypoxia decreases them.[8,9]

Fetal breathing is essential to structural development. When functional breathing movements are impaired by phrenic nerve section or the constricted intrauterine environment associated with oligohydramnios, pulmonary hypoplasia results.[10-12]

While the exchange of amniotic fluid has been demonstrated in fetal sheep by use of intratracheal flow sensors,[2,13] its presence in humans could not be confirmed until Doppler techniques were applied to the larynx and trachea. Our studies indicated that in the trachea, where flow has minimal turbulence, peak inspiratory and expiratory velocities are similar and on the order of 0.1 to 0.2 m/s. Of interest are the symmetric configurations of the inspiratory and expiratory flow curves. Inspiration is an active process resulting from contraction of the diaphragm and chest wall musculature. Expiration, in postnatal life, is the product of the passive recoil of these structures and of the pulmonary alveoli.[14] The symmetric nature of fetal inspiratory and expiratory flow curves suggests that fetal exhalation, like inspiration, is an active process. This is logical, as the fetal chest wall and diaphragm are far more compliant than those of the adult, and alveolar surface tension, a major factor in postnatal elastic recoil of the lung, is absent in the fluid-filled lung of the fetus.

Expansion of the pharynx with inspiration was demonstrated on transverse fetal imaging. This represents anterior displacement of the tongue base and outward movement of the lateral pharyngeal walls. Contraction of the geniohyoid, thyrohyoid, and sternohyoid muscles in synchrony with phrenic nerve activity has been demonstrated in experimental animals, suggesting their role as accessory muscles of respiration.[15,16] Their combined action probably contributes to the increase in the anteroposteri-

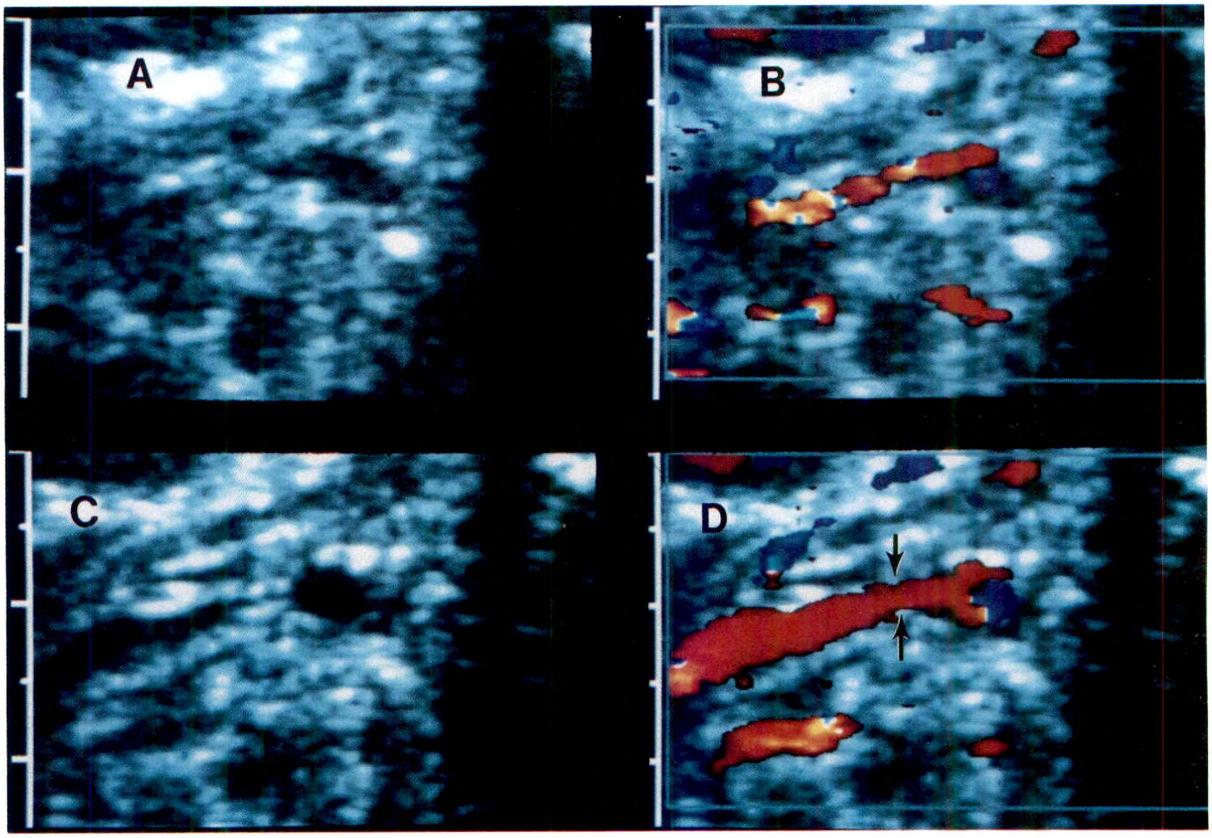

Fig 4. Coronal ultrasound images of fetal larynx in utero. A) Glottis narrows in preparation for expiration. B) Same as A with Doppler ultrasound. Expiratory flow (red) is just beginning. C) Midexpiration. Glottis is still narrow. D) Same as C with Doppler ultrasound. Maximum expiratory flow. Turbulence is absent in trachea and subglottis (pure red). Vocal folds (arrows) indent flow stream.

or dimensions of the pharynx. Lateral expansion should, on an anatomic basis, represent the action of the stylopharyngeus muscles. These muscles are particularly prominent in the fetus and infant. They arise from the styloid processes of the temporal bones and fan out to insert on an aponeurosis with the inferior constrictor. Bosma[17] has speculated about the possible function of the stylopharyngeus as an accessory muscle of respiration.

Respiratory activity of the pharynx has been observed postnatally. Expansion of the pharynx is a well-known radiographic sign in pediatric upper airway obstruction.[18] Further, enlargement of the anteroposterior dimensions of the pharynx has been observed on lateral cineradiographs during the inspiratory phase of the infant cry.[19] Thus, the fetus's exaggerated pharyngeal opening resembles that seen in infants breathing against resistance. It is possible that respiratory exchange of pulmonary and amniotic fluid, with their increased viscosity compared to air, is analogous to forceful respiration in the infant in terms of pharyngeal reflex activity.

The third-trimester fetus shows precise coordination of laryngeal opening with inspiration. The 100-millisecond delay between vocal cord abduction and the onset of inspiratory flow is similar to that seen in adults, suggesting a mature reflex arc.[20,21] The approximation of the vocal cords at the onset of expiration, an important factor in the control of expiratory rate and in the maintenance of lung inflation in postnatal life,[22,23] is present in the older fetus. It is possible that incoordination of laryngeal movements earlier in gestation contributes to the uneven respiratory movements seen in the young fetus.

As more is learned about the physiology of the human fetus, patterns of development emerge. Protective reflexes, including the withdrawal from noxious stimuli, can be identified in the first trimester,[24] while more subtle responses, such as the blink-startle response to vibration or sound, are not consistent until the latter part of the second trimester.[25] This rapid emergence of measurable fetal reflexes during the latter part of the second trimester parallels the accelerated cerebral cortical growth occurring at this time.[26] It is not surprising, then, that refinements in the respiratory function of the larynx should appear during this period.

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7TH WORLD CONGRESSES FOR BRONCHOLOGY & BRONCHOESOPHAGOLOGY

The 7th World Congresses for Bronchology & Bronchoesophagology will be held Sept 28-Oct 2, 1992, at the Mayo Clinic and Mayo Medical Center in Rochester, Minnesota. For further information, contact Udaya B. S. Prakash, MD, Secretary-General & Director, 7th WCB & WCBE, East-18, Mayo Clinic, Rochester, MN 55905.

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SQUAMOUS CELL CARCINOMA IN AN INVERTED PAPILLOMA OF THE BUCCAL MUCOSA

PETER V. BOESEN, MD
ROBERT A. ROBINSON, MD, PHD
MICHAEL J. LASZEWSKI, MD
DOUGLAS E. DAWSON, MD
IOWA CITY, IOWA

Inverted papillomas of the oral cavity are rare lesions. Although in the seven oral cases previously reported the lesions were benign, approximately 10% to 15% of inverted papillomas of the nasal cavity and paranasal sinuses develop or are associated with squamous cell carcinoma. This report presents a case of squamous cell carcinoma arising in an inverted papilloma of the buccal mucosa. Histologically, this lesion demonstrated the morphologic features of inverted papilloma in the superficial portion, and squamous carcinoma in deeper sections. This case suggests that although rare, inverted papillomas of the oral cavity should be considered potentially malignant or capable of harboring a malignancy.

KEY WORDS — buccal mucosa, inverted papilloma, squamous cell carcinoma.

INTRODUCTION

An oral papilloma is a benign outgrowth of the epithelium that is quite common, can occur anywhere in the oral cavity, and has no age group predilection.[1] Microscopically, it presents as an exophytic, fingerlike growth of squamous mucosa surrounding a central connective tissue core. Papillomas that exhibit an endophytic or inverted pattern of growth are rare, relative to the exophytic type, but have been described on the skin and in the nasal cavity and paranasal sinuses, urinary bladder, minor salivary glands, lacrimal sac, renal pelvis, and posterior pharyngeal wall.[1-8] In the oral cavity these lesions have also been termed inverted ductal papilloma.[5] Inverted papillomas of the nasal cavity and paranasal sinuses have developed into squamous cell carcinomas in 10% to 15% of cases.[9] These lesions in the oral cavity, on the other hand, have not been associated with carcinoma.[1,10,11] Although the reported cases are few, the previous reports have stressed the apparent benign behavior of these rare tumors compared to their counterparts in the nasal cavity and paranasal sinuses. This report presents the first case of squamous cell carcinoma arising within an inverted papilloma of the buccal mucosa.

CASE REPORT

A 76-year-old man was referred for evaluation and treatment of an ulcerated, painful lesion of the left posterosuperior buccal mucosa. This lesion had been present for approximately 6 months as a slowly enlarging mass. The patient's medical history was significant for radiation exposure to the neck for treatment of cystic acne as a teenager, a lack of tobacco exposure, and moderate alcohol use. Physical examination revealed a 2 x 2-cm firm, centrally ulcerated lesion on an erythematous, indurated base posterosuperior to Stensen's duct. The salivary flow from Stensen's duct was normal, and his facial nerve function was normal bilaterally. The remainder of the head and neck examination findings, with the exception of carious maxillary dentition and an ill-fitting lower denture, were normal. The mass was excised with primary closure of the mucosal defect. The postoperative course was uneventful, and the patient is free of disease 8 months after surgical treatment.

PATHOLOGY

The initial incisional biopsies showed areas of proliferating nonkeratinizing squamous epithelium forming nodular aggregates and thin ribbons of epithelium (Fig 1). In the majority of the biopsies the epithelium was basaloid squamous epithelium with several areas more suggestive of transitional cell epithelium. Focally cytologic atypia characteristic of carcinoma in situ was present with nuclear irregularity and hyperchromasia, cell crowding, and increased mitotic activity. The adjacent submucosa was edematous and contained an admixture of chronic inflammatory cells; however, invasive neoplasm or stromal desmoplasia was not identified.

The excisional biopsy specimen measured 3.2 x 2.3 x 2.1 cm and contained a centrally located 1.3 x 1.2-cm umbilication with an irregular mucosal surface and focal ulceration. The vertical measure of the neoplasm was 2.1 cm from the surface and it extended to within a few millimeters of the deep margin. The histologic features of the superficial portion were similar to those of the incisional biopsy specimens, with proliferating ribbons of bland non-

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From the Departments of Otolaryngology–Head and Neck Surgery (Boesen) and Pathology (Laszewski, Robinson), The University of Iowa Hospitals and Clinics, and Otologic Medical Services (Dawson), Iowa City, Iowa.

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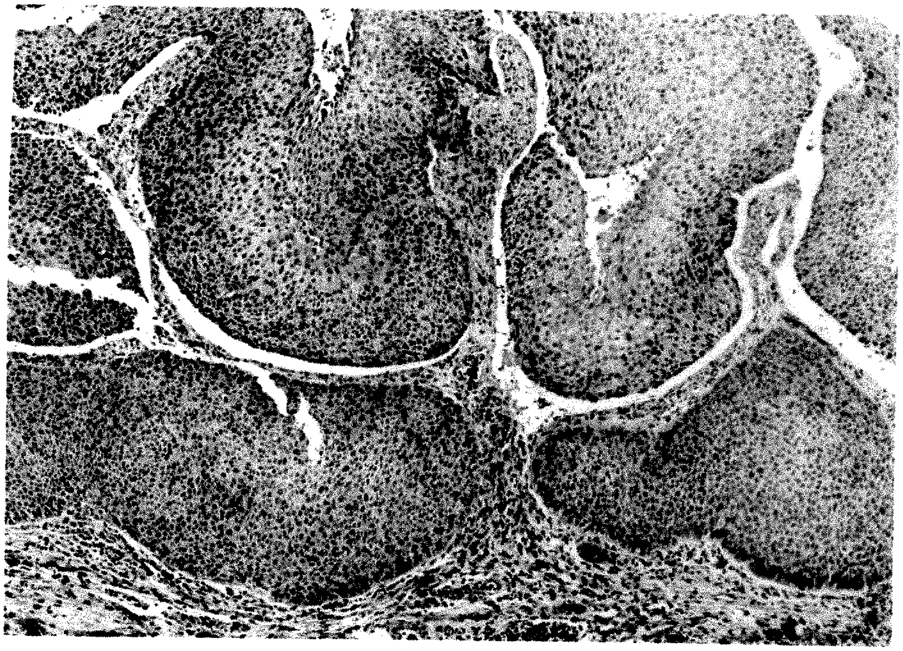
REPRINTS — Douglas E. Dawson, MD, 540 E Jefferson St, Iowa City, IA 52245.

Fig 1. Initial incisional biopsy material showing nodular aggregates of predominately nonkeratinizing squamous epithelium (original x40).



keratinizing squamous epithelium (Fig 2A). The surface proliferation was a combination of exophytic and endophytic growth, giving an irregular appearance to the buccal mucosa. The endophytic growth pushed downward; however, in most of the areas, connection with the surface epithelium was identified. The lower three quarters of the tumor demonstrated an invasive pattern, with trabeculae and small cords of infiltrating squamous epithelium with associated stromal desmoplasia (Fig 2B). A

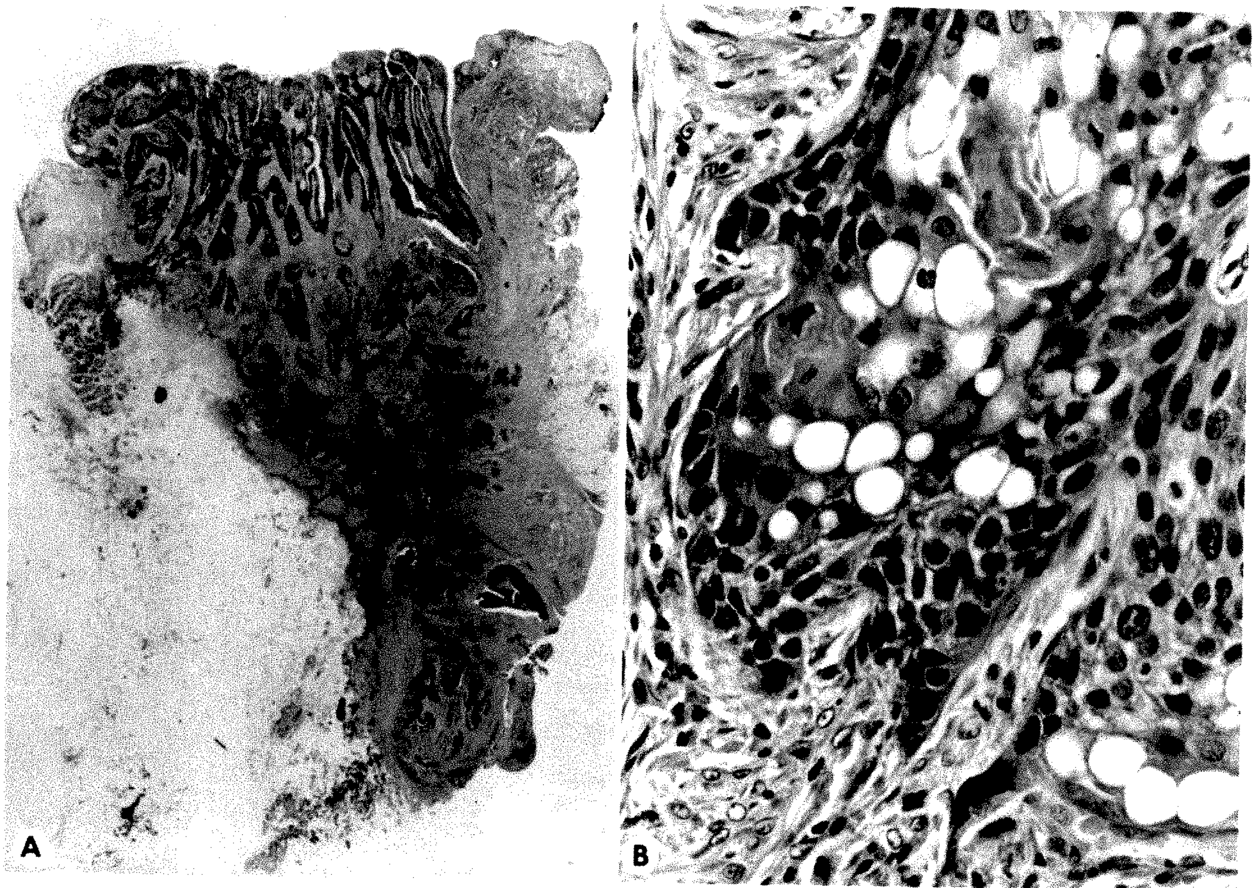


Fig 2. Excisional biopsy specimen. A) Superficial portion of inverted papilloma portion is seen with transition to invasive squamous carcinoma in lower portion (original x10). B) Invasive squamous carcinoma component is evidenced by marked nuclear atypia with desmoplastic response (original x100).

gradual progression in cytologic atypia and keratinization was present from the surface to the deeper invasive component. The tumor infiltrated in a distinct vertical linear arrangement. The flanking oral mucosa was normal buccal squamous epithelium without intraepithelial neoplasia.

DISCUSSION

The origin of inverted papillomas of the nose and paranasal sinuses is thought to be from schneiderian epithelium, a neuroectodermally derived epithelium. The cell of origin of inverted papillomas within the oral cavity is not definitely known, although White et al[5] suggest an origin from reserve cells within salivary gland ducts. These authors base their opinion in part on the finding of adjacent salivary gland duct epithelium in their reported cases of inverted papillomas. We were unable to demonstrate residual ductal epithelium in our case, although not all of the cases reported by White et al[5] showed this feature either. These authors have termed these lesions inverting ductal papillomas. We do not disagree with this terminology and believe it has merit.

The frequency of malignancy in oral inverted papillomas is unknown because of their rarity. This is the first reported case of malignancy arising in an inverted papilloma of the oral cavity. Thus, we believe that inverted papillomas of the oral cavity must be considered either to be premalignant or to harbor an associated carcinoma in an as-yet-unknown percentage of cases.

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FIRST INTERNATIONAL SKULL BASE CONGRESS

The First International Skull Base Congress will be held June 14-20, 1992, in Hanover, Germany. For further information, contact Madjid Samii, MD, Professor and Chairman of Neurosurgery, Medical School Hanover, Neurosurgical Clinic, Hospital Nordstadt, Haltenhoffstr 41, D-3000 Hanover 1, Germany; phone 0049-(0)511-7638245 or 623151, FAX 0049-(0)511-7638606.

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REMODELING PATTERNS IN THE BONY OTIC CAPSULE OF THE DOG

MADS SØLVSTEN SØRENSEN, MD
MARTIN BALSLEV JØRGENSEN, MD
POUL BRETLAU, MD
COPENHAGEN, DENMARK

Quantum-type bone remodeling was studied in undecalcified temporal bones and long bone specimens from adult mongrel dogs by means of combined microradiography, osteofluorochrome labeling, and osteoid staining. The overall turnover rate of capsular bone was estimated to be low compared to that of extracapsular compact bone. Evolving secondary osteons were distributed centrifugally relative to the perilymphatic space. Moreover, a zone of bone tissue enclosing perilymphatic spaces was found completely devoid of evolving secondary osteons. Throughout the otic capsule, segmentary perivascular foci of resorption and formation were present. These findings indicate that remodeling of capsular bone is subject to sustained local inhibition. The significance of this conclusion is considered with special reference to otosclerosis.

KEY WORDS — blue mantles, bone resorption, fluorescent dyes, histology, microradiography, otosclerosis, undecalcified processing.

INTRODUCTION

Human otosclerosis is a localized disorder of bone resorption and formation entirely restricted to the bony otic capsule. In order for us to understand pathologic capsular remodeling, the normal pattern of bone turnover in the temporal bone must be determined.

Most of our present knowledge of temporal bone remodeling derives from studies of decalcified human and animal material. Unfortunately, decalcified sections primarily provide indirect information on the dynamic processes of bone, since they can display only the result of these processes. Direct observation of the remodeling process itself requires sections of undecalcified bone, labeled in vivo with hydroxyapatite-seeking fluorochromes used as bone tissue time markers. This technique, listed by a human temporal bone workshop report as a potential area for future research,[1] was recently applied to studies of temporal bones of rats and pigs. The results suggest the presence of a local mechanism controlling modeling and remodeling of the bony otic capsule in these animals.[2,3]

The aim of the present study was to reconsider, in a different species, the proposed pattern of remodeling, unique among compact bone tissues of the skeleton, by means of a labeling schedule designed to monitor bone formation during a sustained time period. Compared to short-term labeling, this method increases the total number of labeled elements and facilitates discrimination of morphologically different structures. The approach to remodeling is based on the quantum concept as outlined by Frost[4] and Parfitt.[5,6]

MATERIALS AND METHODS

Animals. A total of 13 mongrel dogs, 3 years of age, were used. Five dogs selected at random served as unlabeled controls. The labeling schedule was partly determined by the concomitant use of the animals for experimental orthopedic surgery. Three dogs were labeled with tetracycline hydrochloride 20 mg/kg per day given perorally for 12 weeks until the dogs were painlessly killed. These 3 dogs received two additional intravenous injections of calcein green (Sigma) 15 mg/kg at 9 and 8 weeks before killing (that is, at day 21 and 28 of the tetracycline labeling period), and two intravenous injections of xylenol orange (Sigma) 50 mg/kg at 9 days and 2 days before killing. The remaining 5 dogs were similarly labeled with tetracycline for 30 days and received additional intravenous injections of calcein green at 9 days and 2 days before killing (that is, at day 21 and 28 of the tetracycline labeling period). Housing and feeding were according to standard animal care protocols, and the study was licensed by the national board of animal experiments. The dogs were killed with intravenous pentobarbital. The temporal bones were removed en bloc, trimmed, and immersion-fixed in 10% neutral-buffered formaldehyde along with pieces of radial diaphysis.

Embedding. After dehydration in ethanol and defatting in ether/acetone 1:1, the specimens were immersed in pure methyl methacrylate (BDH, Poole, England), agitated, and vacuum-extracted. Polymerization was done in a water bath at 32°C and took 2 weeks.

Sectioning. Sections (400 μm) were cut with an

From the Otopathology Laboratory, Department of Otolaryngology-Head and Neck Surgery, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. This study was supported in part by the Skouby Foundation and by the Oticon Foundation.

REPRINTS — Mads Sølvsten Sørensen, MD, Dept of Otolaryngology-Head and Neck Surgery, F 2073, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.

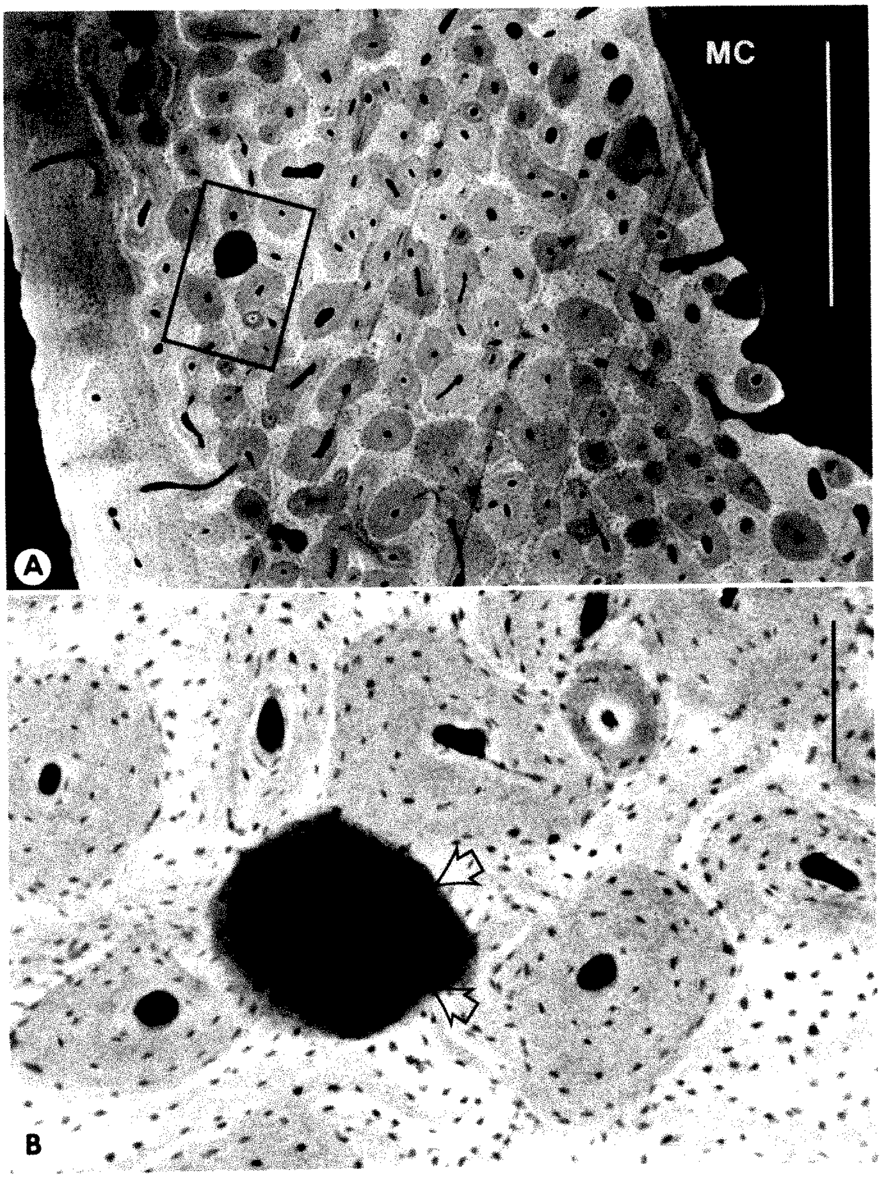

Fig 1. A) Microradiograph. Diaphyseal cross section with secondary osteons. MC — marrow cavity, bar — 1,000 μm. B) Inset from A. Notice lower density of newly formed osteonal bone (arrows). Bar — 100 μm.

Accutom-2 (Struers, Copenhagen) automatic metallographic cutting machine. As approximately 600 μm was removed by the rotating saw during each cut, the block was advanced in 1,000-μm steps, and a total of 9 to 11 horizontal sections containing capsular bone could be obtained from each temporal bone (one section per millimeter of capsule). Both longitudinal and transverse sections were prepared from diaphyseal bone. All sections were handground on a Knuth-Rotor grinding machine (Struers) to a thickness of 100 μm while fixed on a specimen-holder by double-faced tape, and subsequently removed with hexane.

Microradiography. Sections (100 μm) were contact-microradiographed at 19 kV in a Machlet OEG-50 on Kodak spectroscopic plates type 649-0. All sections were then mounted on Plexiglas slides (Kulzer-Exakt, Germany) with cyanoacrylic glue B 210 (3M) in a precision adhesive press (Kulzer-Exakt) and ground by hand to a final thickness of 20 to 40 μm.

Fluorescence. Unstained coverslipped sections from one unlabeled dog and eight labeled dogs were examined with a Leitz Orthoplan microscope by means of a D filter block in the Ploemopak epi-illuminator. In photomicrographs the red fluorescence of xylenol orange was enhanced by double exposures with D and N2 filters on Kodak Ektachrome 160 or Kodacolor Gold 400.

Staining. Sections from four unlabeled dogs and selected sections from labeled dogs, which were examined in the fluorescence microscope without coverslipping, were stained with modified Stevenel's blue.[7]

Resorptive surfaces appear uneven and characteristically have a high mineral density on microradiographs. In sections stained with Stevenel's blue, osteoclasts and mononuclear phagocytic cells can be identified. Formative surfaces are smooth and bordered by lamellae of low density, because secondary (final 25%) mineralization of newly formed bone requires several months for completion. The osteofluorochromes are incorporated into the mineralization front of formative surfaces along with calcium phosphate. When they are administered in vivo, and undecalcified sections are examined under UV light, surfaces on which formation was taking place at the time of single-dose administration show a narrow band of fluorescence, whereas daily administration for a sustained period labels the entire amount of new bone produced during the labeling period. On stained sections, formative surfaces are covered by osteoblasts on a greenish osteoid seam bordering the pink mineralized bone.

RESULTS

The long bone specimens showed normal quantum-type osteonal remodeling distributed at random across the mid-diaphyseal cortex. Secondary osteons were uniform in size, orientation, and shape. Figures 1 and 2A,B show the typical cross-sectional morphology of a bone remodeling unit (BRU).

In all microradiographs the overall density of the bony otic capsule was clearly higher than that of extracapsular bone in the same section. The shift in mineral content took place at the sutural connections with the surrounding cranial bones or quite abruptly at the line at which the lateral part of the capsule connected directly with the tympanic bone. Osseous globules and interglobular spaces were highly mineralized.

In the fluorescence microscope the otic capsule appeared dark, the amount of labeled (newly formed) bone being clearly much less than in the neighboring cranial bones or in long bones. Quantification of absolute turnover rates with routine bone histomorphometric methods was not attempted, since current methods depend on several stereologic preconditions, established so far only in compact bone tissues quite different from capsular bone. No evidence of formation or resorption was found in osseous globules, interglobular spaces, stapes, or modiolus, or at any inner surface of the perilymphatic space. Bone formation was noted at the periosteal capsular surface facing the posterior cranial fossa or lining the internal auditory canal.

By combining fluorescence microscopy with corresponding microradiographs, we identified a small number of evolving secondary osteons (BRUs) in the periosteal capsular layer and the peripheral part of the endochondral layer (Figs 2C and 3). These BRUs, although limited in number, had a normal size and shape and were often connected with the capsular surface facing the tympanic cavity or the sutural connection with adjacent cranial bones, at which active resorption and formation were frequently visible. This activity was most pronounced around the semicircular canals (Figs 2C and 3), anterior and medial to the cochlea, adjacent to the internal auditory canal, and lateral to the genu of the facial nerve. Regular BRUs were at least 400 μm away from any perilymphatic space, and in fact only three small developing osteons were observed at this minimal distance in a total of 154 sections from 16 labeled temporal bones. Generally the diameter of BRUs decreased from the normal size of 150 to 200 μm found in the peripheral part of the capsule to about 60 to 80 μm at the most central position recorded.

In all capsular layers, including the area immediately surrounding perilymphatic spaces, in which no osteonal remodeling was evident, some interesting segmentary elements were seen. Whereas the majority of vascular canals had a smooth lining, segments of various lengths having a slightly larger diameter were lined by a rough-surfaced, highly mineralized matrix, giving the canal a rugged appearance (Fig 4A). In stained sections, corresponding segments occasionally contained large mononuclear cells in the perivascular space, but no osteoclasts were seen. The lining matrix of most of these segments was not labeled by osteofluorochromes (Fig 2D), but a large number of vascular canals had segments of similar length and distribution, with a smooth canal enclosed in a sheath of labeled bone (Fig 2E). In corresponding microradiographs the mineral content of labeled bone was low (Fig 4B), and a greenish osteoid seam was evident in stained sections. Most of these perivascular sheaths extended less than 15 μm into the surrounding capsular bone, but in peripheral capsular parts the diameter of segments ranged from the minimum up to normal osteonal size.

DISCUSSION

Internal remodeling is the turnover of bone tissue at the histologic level. It is essentially a quantum phenomenon, acting on inner and outer bone surfaces as disseminated processes of minute destructions that are followed by reconstructions. When these anatomically discrete foci of remodeling, the BRUs, are activated in compact bone, osteoclasts appear on a bone surface and erode into the old bone, leaving behind a canal containing proliferating blood vessels. This canal is soon lined by osteoblasts, which subsequently deposit concentric lamellae of bone, refilling the tunnel from the circumference toward the center. The resulting new bone structural unit is a secondary osteon or haversian system.[5,6] From this general scheme of activation leading to resorption leading to formation, it is obvious that in remodeling of compact bone, resorption must always precede formation. The source of the osteoclast responsible for resorption is

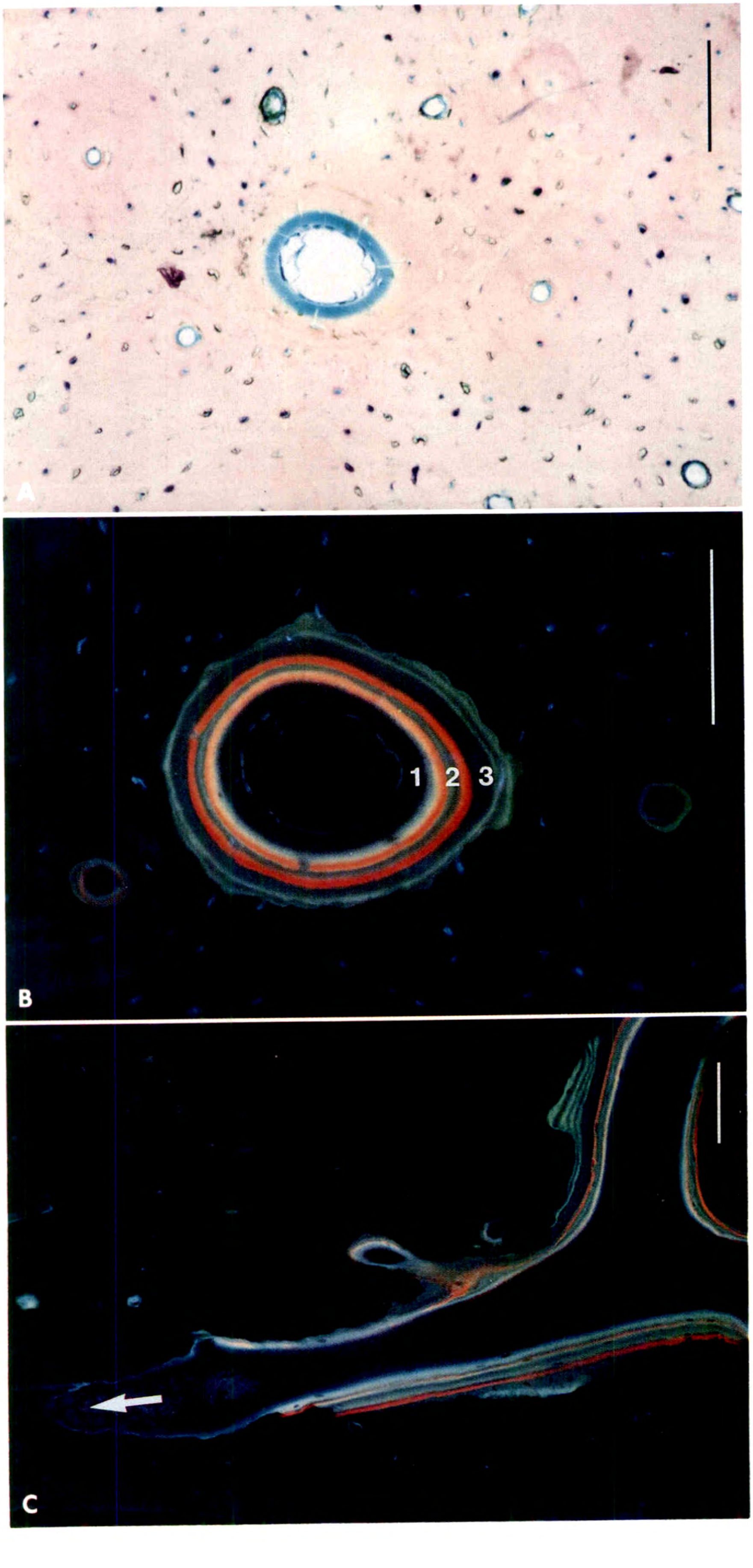

Fig 2. Bars — 100 μm. A) Stained section, same as Fig 1B. Mineralized bone is pink, osteoid is green, and cells are blue. B) Fluorescence micrograph, same as Fig 1B. No calcein green is present. 1 — osteoid, 2 — xylenol orange, 3 — tetracycline. C) Fluorescence micrograph, head of invading bone remodeling unit from Fig 3. Arrow — direction of movement. (Continued on next page.)

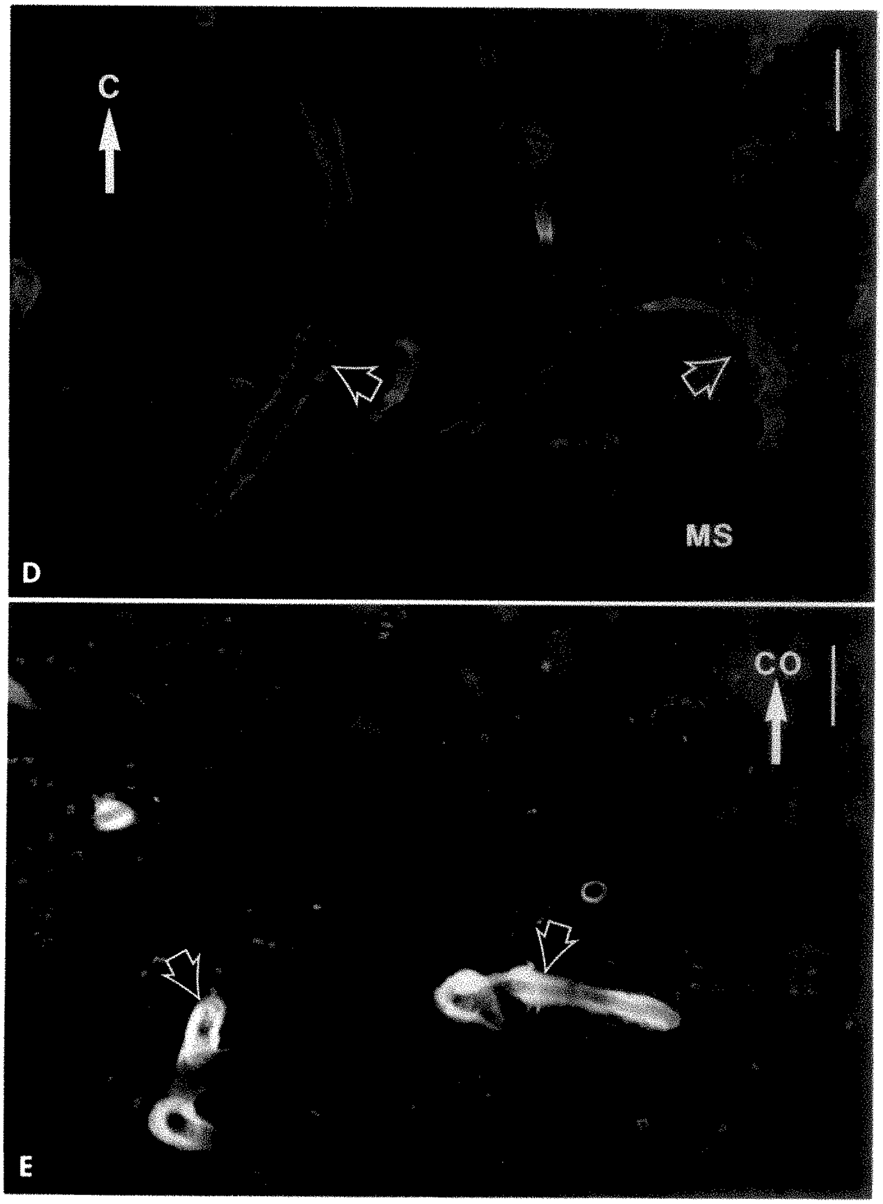

Fig 2, continued. D) Fluorescence micrograph, same as Fig 4A. MS — marrow space, C — direction toward cochlea, arrows — rugged vascular canal segments. E) Fluorescence micrograph, same as Fig 4B. CO — direction toward cochlea, arrows — sheath of labeled bone in smooth low-density canal segments.

now generally agreed to be the bone marrow.[8-11] Immature mononuclear phagocytes carried to the bone surface by the bloodstream are in some as yet unknown way activated locally, attach to the perivascular matrix, and commence resorption. As more circulating precursors are recruited, they will fuse to form a syncytium — the osteoclast, which progressively incorporates and loses nuclei in a continuous renewal of nuclear components.[8,10] For this reason any BRU must initially arise within a Volkmann's canal or within an existing haversian canal. The resorption tunnel might extend along this preexisting canal like a peristaltic wave. However, normally BRUs diverge from the canal in which they developed and tunnel into solid bone.[6]

The present observations on remodeling units in long bones and cranial bones, including the tympanic bone, are quite in agreement with this concept (Figs 1 and 2A,B).

In capsular bone, fully developed BRUs are distributed centrifugally relative to perilymphatic spaces. They are found almost exclusively in the outskirts of the endochondral layer or in the periosteal layer, from where they often connect to osteonal systems of normal cranial bone (Fig 3). These BRUs most likely are activated outside the otic capsule and are fully developed when they enter capsular bone. However, whereas secondary osteons of compact bone normally have a total length of several millimeters, these BRUs are apparently always terminated shortly after their entry into the otic capsule. Although remodeling activity is subject to wide differences from one region of the skeleton to the other,[12] the existence of a 400-μm-wide zone of bone enclosing perilymphatic spaces, in which no quantum remodeling occurs, is quite unique. Moreover, remodeling activity of the capsular bone is generally clearly reduced even compared to that of mid-diaphyseal long bone, in which

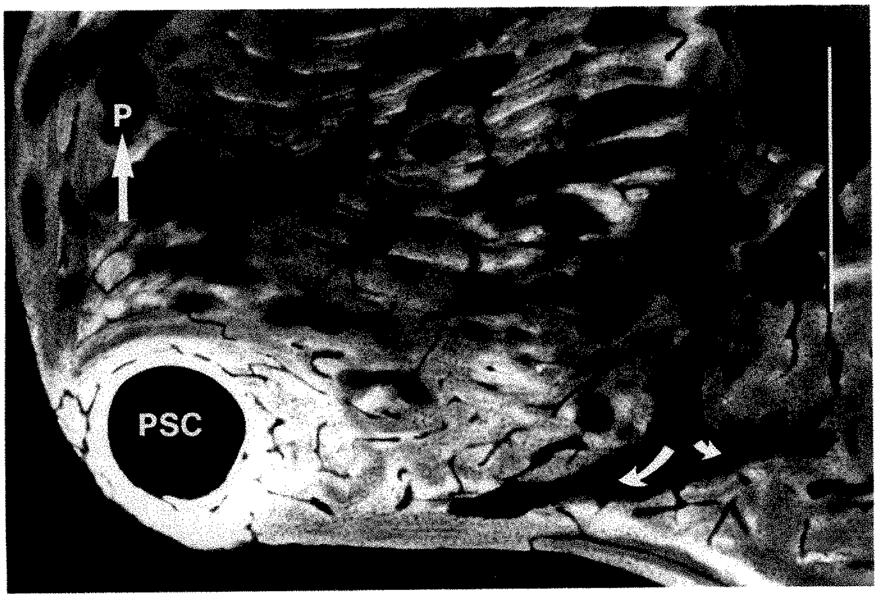

Fig 3. Microradiograph. Left bony otic capsule. Arrows are inside invading bone remodeling unit. P — posterior, PSC — posterior semicircular canal, bar — 1,000 μm.

the turnover rate is at a minimum.[12]

The segmentary elements of the vascular canals seem to represent different phases of what could be described as "attempted remodeling." That is, the rugged, unlabeled, and wider segments (Figs 2D and 4A), in which extravascular mononuclear cells are occasionally found, are sites of activation inside the otic capsule itself. Mononuclear phagocytic cells are activated and commence resorption along the lining wall matrix. However, for some reason the cells are unlikely to fuse, resorption is ineffective, and no regular cutting cone develops. Instead, resorption soon ceases, leaving only a slightly excavated canal segment, to be repaired subsequently with a sheath of new bone of immature type. This process accounts for the small segments enclosed in a sheath of labeled, low-density bone (Figs 2E and 4B). As judged from the distribution and diameter of labeled segments, remodeling tends to normalize toward the periphery of the capsule, where labeled perivascular segments of near-normal osteonal calibers are found.

The perivascular activities of resorption and formation described here differ from normal quantum-type bone remodeling, since activation does not lead to evolution of regular BRUs. The segmentary activity can only provide for renewal of the bony membrane immediately surrounding existing vascular canals, leaving the majority of capsular bone unaffected — hence the term "attempted remodeling."

Perivascular lesions of the decalcified otic capsule have been studied in experimental animals and humans by many researchers using both light and electron microscopy.[13-19] Blue mantles consist of fingerlike resorption spaces subsequently filled with bone, which is rich in glucosaminoglycans. They are found in many temporal bones and are distributed just like the BRUs of the present study. Limiting sheaths (*grenzscheiden, blaue säume*) are blue-staining (hematoxylin and eosin) bony membranes lining some vascular canals. Blue mantles and limiting sheaths are often considered separately, but the limiting sheaths are exaggerated near vascular mantles,[19] and transitional forms are in fact seen.[13]

On the basis of the present observations, we suggest that limiting sheaths and vascular mantles belong at either end of a range of perivascular structural elements of the otic capsule, which may be viewed in the light of quantum remodeling and "attempted remodeling." That is, the limiting sheath is the result of an aborted activation of remodeling, whereas the vascular mantle represents the imprint of a full-blown BRU. The latter is either activated and developed inside capsular bone or introduced from surrounding cranial bones. Regardless of their origin, full-sized BRUs are normally found only at some distance from the perilymphatic space.

Our observations are in agreement with those of Hawke and Jahn,[20] who studied undecalcified sections from human temporal bones labeled with tetracycline during adult life and found similar perivascular labeling of capsular bone. However, no such perivascular activity was found in studies in which young growing animals were used,[2,3,21] suggesting the role of skeletal age and species in remodeling patterns. The overall reduction of capsular remodeling activity, the centripetal distribution of BRUs, and the existence of a perilymphatic zone of no remodeling call for an explanation. It is unlikely that a quality inherent in endochondral-type bone is responsible, since quantum remodeling can actually take place in this tissue. More likely, capsular remodeling is subject to sustained local control.

It is established that capsular development is sub-

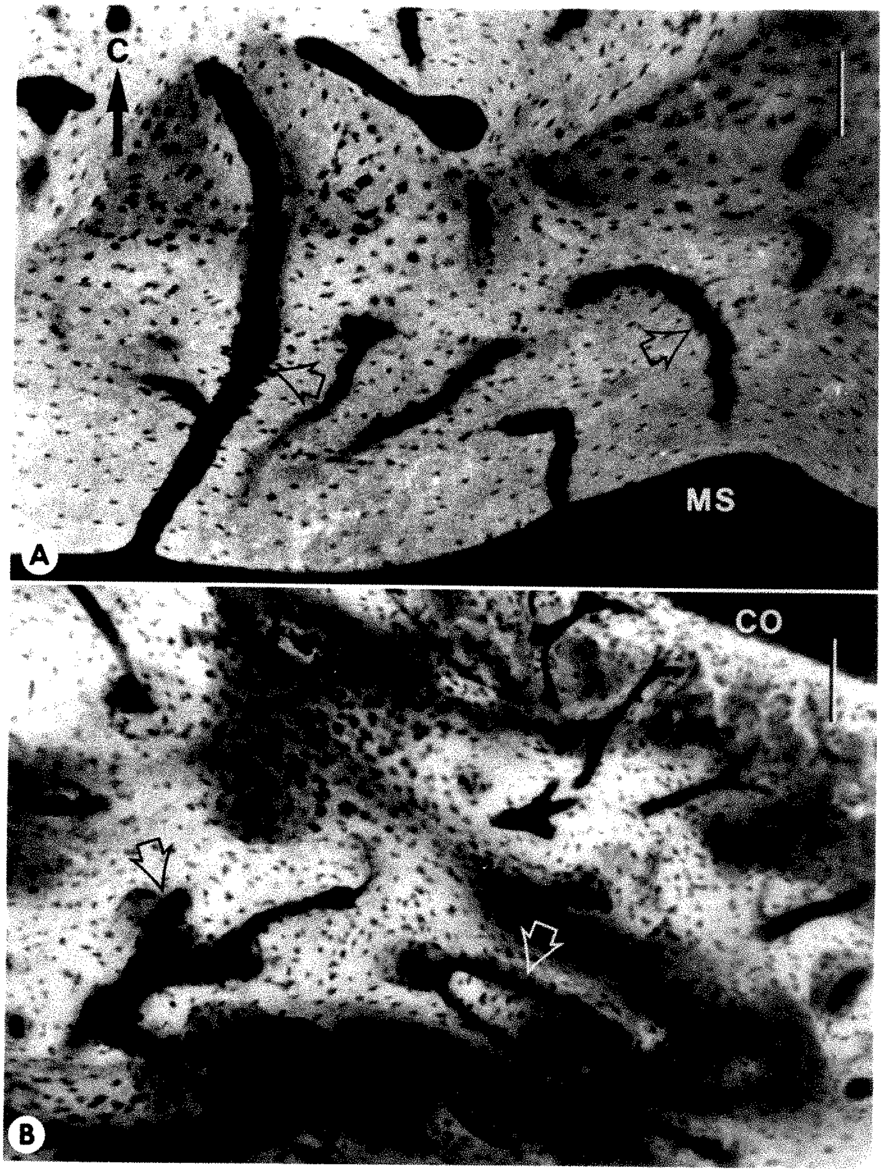

Fig 4. Microradiographs of bony otic capsule ventral to cochlea. Bars — 100 μm. A) MS — marrow space, C — direction toward cochlea, arrows — rugged vascular canal segments. B) CO — cochlea, arrows — smooth low-density canal segments.

ject to reciprocal interaction with the vestibulocochlear end-organ itself.[22,23] Moreover, labyrinthectomy leads to bone formation inside the perilymphatic space,[24,25] in which normally resorption and formation cannot occur, except in otosclerosis[26] or following severe labyrinthine damage by infection, for example.[27,28] Blue mantles are known to be greatly exaggerated in otosclerotic temporal bones, indicating an overall increase in capsular remodeling activity. However, histomorphometric analysis of tetracycline-labeled iliac trabecular bone failed to demonstrate any generalized increase of bone-remodeling rates in otosclerotic patients.[29] We suggest that bone remodeling in the otic capsule is normally subject to sustained local control by a mechanism resident inside the perilymphatic space. Because of this inhibition, normal quantum-type bone remodeling is restricted to the outer parts of the capsule. Closer to the perilymphatic space, remodeling is limited to discrete segmentary activity along preexisting vascular canals. The pathologic remodeling of otosclerosis might well be secondary to a disturbance of such a control mechanism.

The morphologic findings call for future morphometric accounts of the distribution of BRUs and perivascular segmentary elements in relation to the perilymphatic space.

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BILATERAL ARTERIOVENOUS MALFORMATION OF THE MANDIBLE

ROBERT A. SOFFERMAN, MD
BURLINGTON, VERMONT

GORDON W. SUMMERS, DMD, MD
PORTLAND, OREGON

Spontaneous bleeding from the molar gingiva may reflect the presence of a life-threatening vascular malformation. Sporadic reports of exsanguinating hemorrhage in the dental literature warn of the dangers of extraction, although deaths from unrecognized lesions or secondary to mandibular fracture still occur. Arteriovenous malformation (AVM) may be either unilateral or, less commonly, bilateral, and should be suspected in individuals with large lower facial hemangiomata. Two cases of near-exsanguinating hemorrhage from bilateral AVMs are discussed with the long-term management over a 3- to 20-year follow-up. The report underscores the failure of therapeutic embolization and the need for computed tomographic scanning as a corollary to angiography. A newer treatment with direct removal of the AVM and obliteration methods solves the hemorrhagic complications, reduces the potential for steal syndromes, and reduces the potential for recurrence.

KEY WORDS — arteriovenous malformation, hemorrhage, mandible, vascular malformation.

Although relatively rare, arteriovenous malformation (AVM) of the mandible must be well understood early in a diagnostic sequence in order to avoid potentially lethal hemorrhage with either biopsy or tooth extraction.[1] The dental and oral surgical literature provides adequate exposure and awareness; but the limited reference to the condition in head and neck writings allows for ignorance of the magnitude of the clinical problem. The most common initial presentation is spontaneous spurting bleeding adjacent to one of the molars.[2,3] A solid clue to the existence of an osseous vascular malformation of the mandible itself is the frequent presence of an overlying vascular nevus or cutaneous hemangioma.[4] Arteriovenous malformation of the mandible is synonymous with cavernous hemangioma, central hemangioma, and pulsating hemangioma.[5] The radiographic appearance of an osteolytic lesion ipsilateral to the hemorrhage is by no means pathognomonic of an AVM. The differential diagnosis[6,7] also includes ameloblastoma, giant cell lesion, myxoma, dentigerous cyst, sarcoma, fibrous dysplasia, and simple dental granuloma or cyst. Vascular tumors such as hemangiopericytoma[6] and metastatic thyroid carcinoma[8] may have plain radiographic clinical manifestations similar to those of an AVM. It is apparent that there are inherent dangers in managing the lesion principally on the basis of the radiographic features. The lesion requires careful attention to symptoms and signs as well as a battery of diagnostic maneuvers. Lamberg et al[1] have reviewed a group of 11 fatalities from uncontrollable hemorrhage and included a case of bilateral AVM similar to the following two cases.

CASE REPORTS

Case 1. An 11-year-old boy presented to the Medical Center Hospital of Vermont from an outlying emergency room with two episodes of bleeding between the left first and second mandibular molars (Fig 1). Each hemorrhage totalled between 300 and 500 mL. Mandibular films demonstrated bilateral extensive lucencies. Physical examination revealed bilateral pulsatile swelling of the lower facial and upper neck tissues with angiomatous discoloration. Bilateral thrills and bruits over the same distribu-

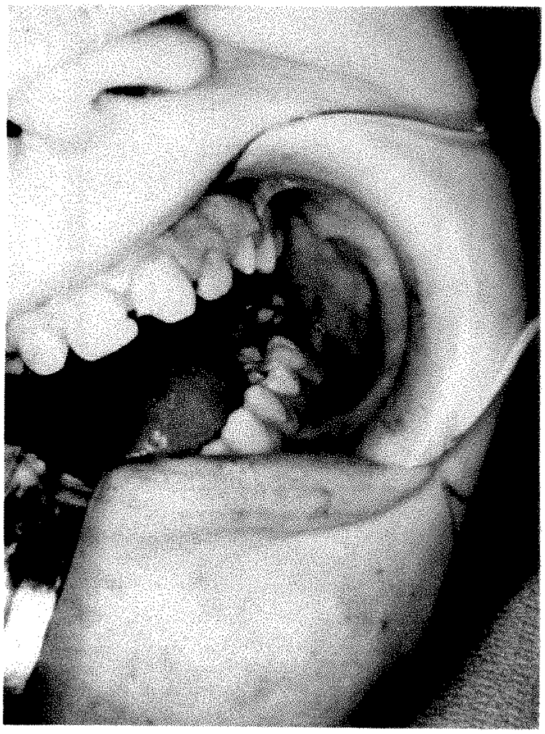

Fig 1. (Case 1) Sentinel bleeding from second molar gingiva.

From the Section of Otolaryngology, University of Vermont College of Medicine, Burlington, Vermont (Sofferman), and the Division of Otolaryngology, Providence Medical Center, Portland, Oregon (Summers).

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REPRINTS — Robert A. Sofferman, MD, 1 S Prospect St, Burlington, VT 05401.

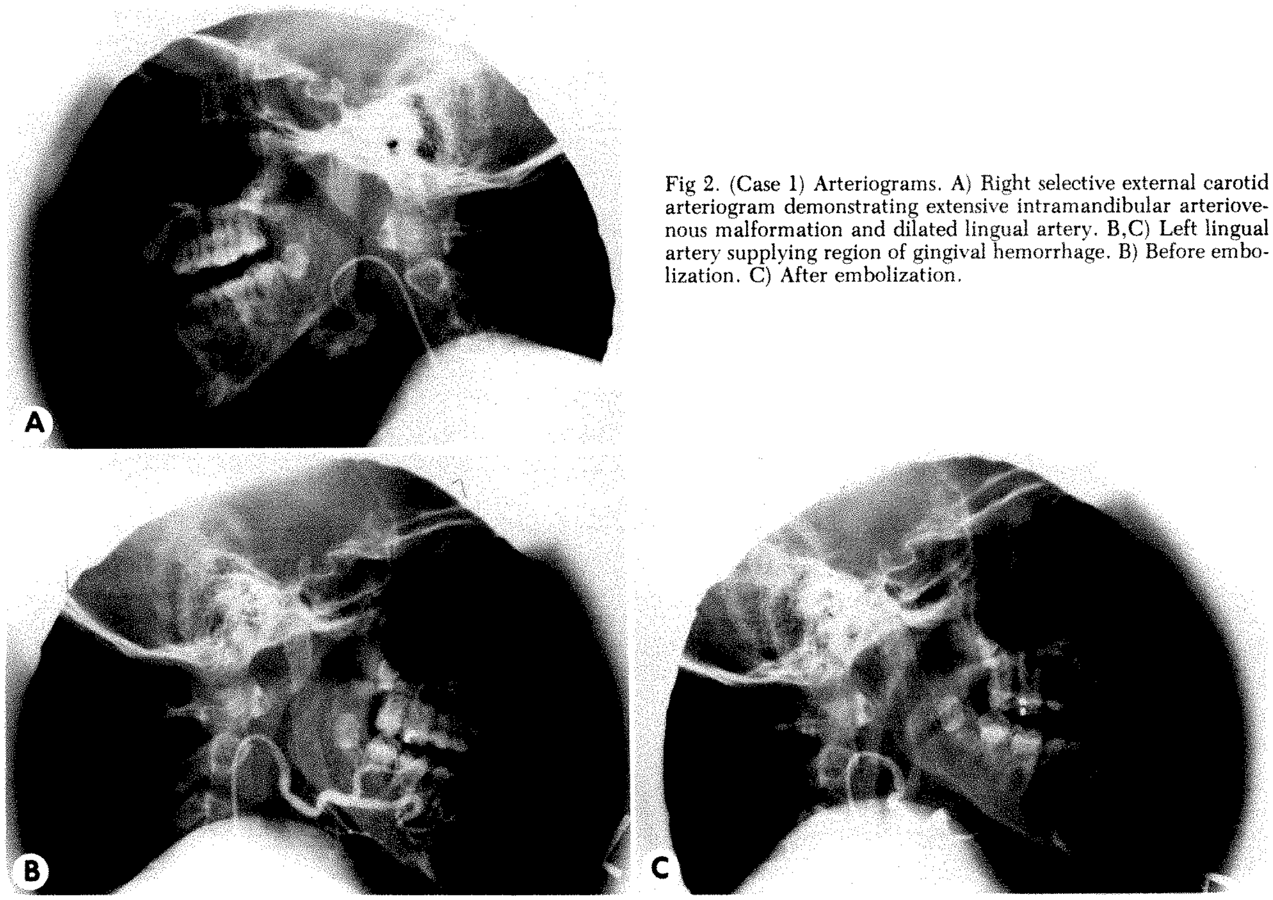

Fig 2. (Case 1) Arteriograms. A) Right selective external carotid arteriogram demonstrating extensive intramandibular arteriovenous malformation and dilated lingual artery. B,C) Left lingual artery supplying region of gingival hemorrhage. B) Before embolization. C) After embolization.

tion were identified along with prominent arterial pulsation at each mental foramen. Emergency angiography (Fig 2A) demonstrated an extensive bilateral vascular network within the mandible and an apparent hypertrophied lingual artery supplying the region of hemorrhage. The lingual artery was obliterated with Gelfoam embolization (Fig 2B,C), but 2 hours later a third significant hemorrhage ensued. A surgical procedure was planned, beginning with endotracheal intubation and removal of the area molar and direct gingival suture ligation.

With extraction, massive hemorrhage developed (1,200 mL in 2 minutes), requiring major changes in orientation (Fig 3A). After generous packing intraorally, a left submandibular incision was performed, providing access to markedly dilated branches of the external carotid system. Lingual, facial, inferior alveolar, and approximal external carotid arteries were ligated, and a visor flap was developed in attempts to control the perforating vessels through the buccal cortical plate. During this maneuver, extensive bleeding occurred with a drop in systolic pressure to 40 mm Hg. A lip-splitting incision and rapid elevation of a mandibular labial flap allowed bone wax obliteration of numerous 3- to 4-mm sievelike vascular conduits between the cheek soft tissue hemangioma and the intramandibular malformation (Fig 3B). The procedure was terminated with a tracheotomy after an 8,000-mL blood loss and persistent oozing from a dilutional coagulopathy. A computed tomography (CT) scan revealed bilateral, central cavitation of the mandible and multiple cortical defects (Fig 4).

One week later, bilateral labial flaps were elevated and the right hemimandible was devascularized in a manner similar to the initial left side. Bilateral buccal plate windows were made in the mandible and the entire AVM was curetted from its interior, angle-to-angle. Cancellous bone and some fat from the iliac crest were used to fill the defect. Blood loss was reduced to 4,000 mL at this procedure, and much of this was reinfused through the use of the cell saver. Bruits and soft tissue pulsations completely disappeared and all bleeding ceased. Over the ensuing weeks, a small orocutaneous fistula and localized infection (alpha and gamma *Streptococcus, Eikenella corrodens*) were controlled with local packing and parenteral clindamycin. A few sequestered bone fragments and localized angiomata required curettage and cautery over the next several months, but no significant hemorrhage or complication has developed over the past 3 years (Fig 5).

Case 2. A 9-year-old boy was referred to the University of Oregon Medical School Otolaryngology Clinic in October 1968 with a 3-month history of intermittent intraoral hemorrhage. The initial bleeding episodes were nocturnal, were of short dura-

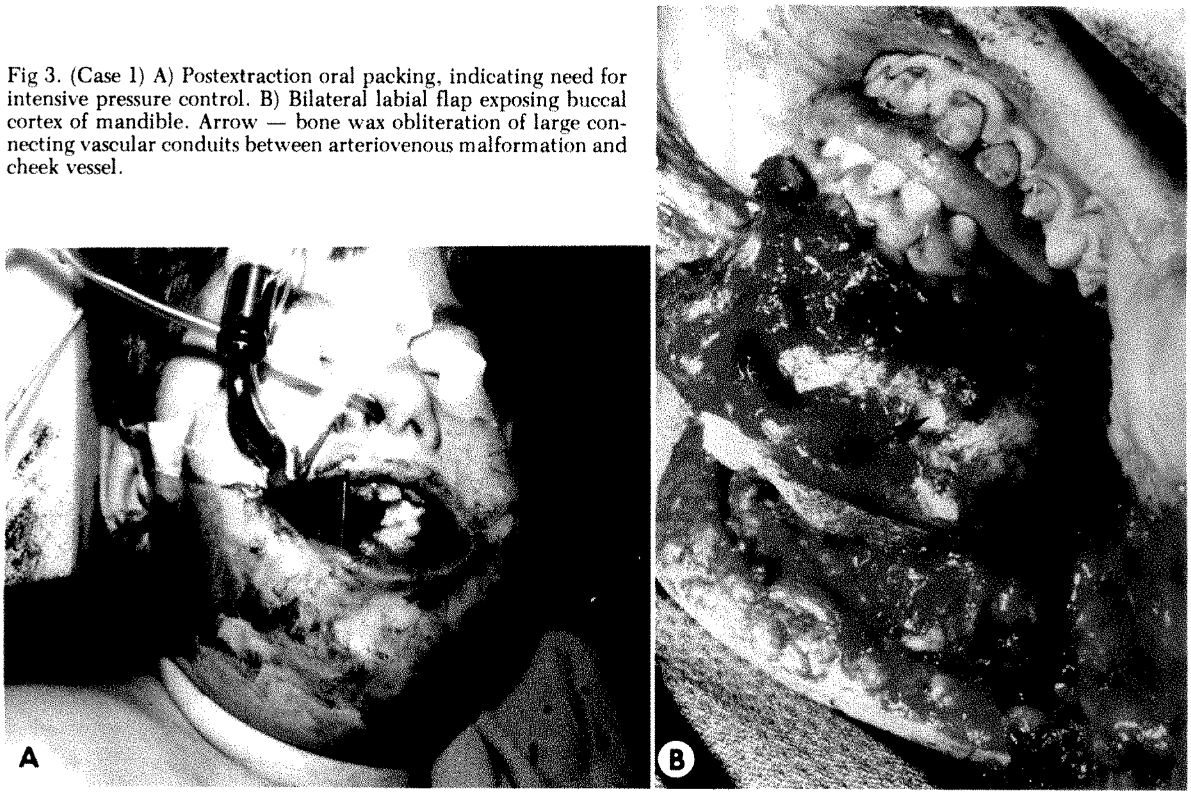

Fig 3. (Case 1) A) Postextraction oral packing, indicating need for intensive pressure control. B) Bilateral labial flap exposing buccal cortex of mandible. Arrow — bone wax obliteration of large connecting vascular conduits between arteriovenous malformation and cheek vessel.

tion, and always ceased spontaneously. A light tan birthmark and several small petechiae were noted on the left cheek. The left mandibular 6-year molar was mobile, with a minimum amount of hemorrhagic-appearing gingival tissue along its buccal surface. The remaining mixed dentition was in excellent condition. Radiographs demonstrated a radiolucency of the left hemimandible from the middle of the ramus to the mental foramen (Fig 6A).

Over the next several weeks, bleeding increased to up to one cup of bright red blood as often as four times daily. At subsequent clinical examination, a bruit and palpable thrill were noted over the left hemimandible, and both were obliterated by compression of the left facial artery. Palpation of the left mandibular 6-year molar produced a brisk 200-mL arterial hemorrhage from around the neck of the tooth. Although the admitting hematocrit was 23%, the hemodynamic status was stable with a pulse of 88 and a blood pressure of 110/54. A transfemoral arteriogram demonstrated a large left hemimandibular AVM with an afferent supply principally from the facial and lingual arteries. The left external carotid was distinctly enlarged.

Three weeks following a decision to manage the child expectantly, recurrent spontaneous hemorrhage developed. On January 10, 1969, the lesion was electively addressed. Through a left submandibular incision, a flap was elevated, exposing the lateral surface of the hemimandible. Upon opening of the periosteum, the buccal cortex overlying the lesion was noted to be perforated with multiple sievelike holes that bled briskly. After bleeding was controlled by bone wax, a large plate of buccal cortex was removed to gain access to the lesion. Profuse bleeding ensued in spite of external carotid artery ligation and was eventually controlled with pressure packing. Curettage of the lesion and packing of the entire osseous cavity with Surgicel gauze provided definitive control (Fig 6B,C). Total blood loss for the procedure was 3,500 mL.

Sixteen months later, hemorrhage from the opposite molar region required readmission and a similar curettage procedure in conjunction with dental extraction. Afferent vessels and the external carotid were also ligated. One month later, additional right hemimandible bleeding required repeat curettage, packing, and further vessel ligation. Eventually, mandibulotomy and division of vessels to the mandible through the myelohyoid and geniohyoid muscles were required. In 1972, the patient experienced daily oozing from the right maxillary molar-premolar area. Four-vessel angiography in 1973 demonstrated a persistent AVM of the right maxilla and mandible with multiple feeding vessels from the left vertebral and internal carotid systems. Right maxillary alveolar ridge excision and antrostomy resolved bleeding from the dental/osseous axis. Over the next 16 years, the soft tissue lesions of the face continued to enlarge with patient growth, but no major bleeding has recurred from the jaws (Fig 6D). Occasional bleeding from intraoral soft tissue hemangiomata has been completely manageable with conservative measures.

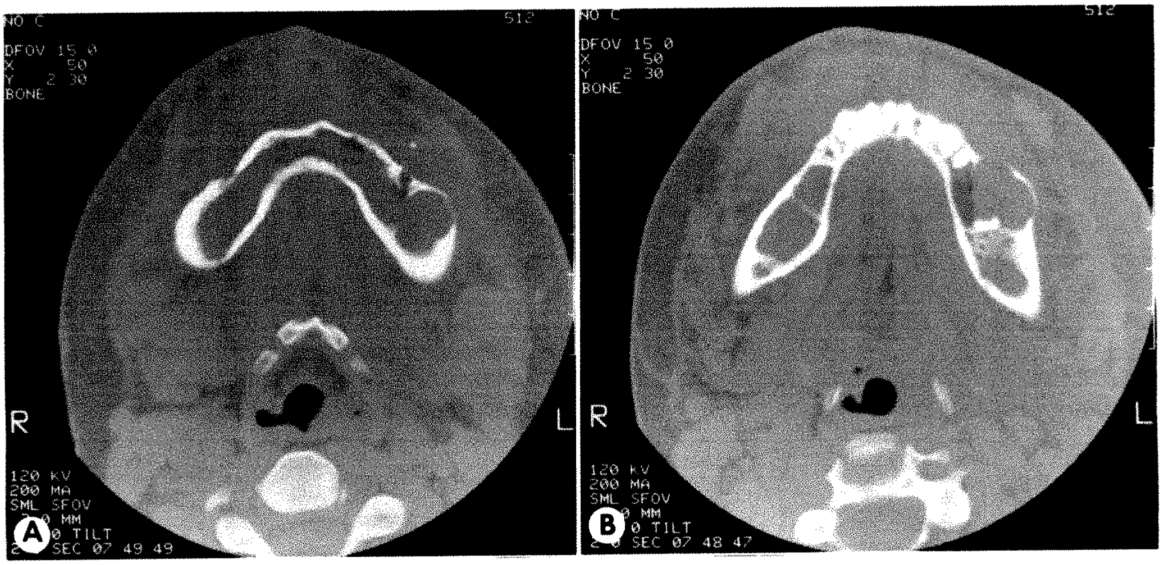

Fig 4. (Case 1) Computed tomograms demonstrating bilateral nature of arteriovenous malformation and buccal cortical defects. A) Inferior aspect of mandibular body demonstrates contiguity of bilateral mandibular defects across midline. B) Mid-upper level of mandibular body demonstrates intact dentition and extension of lytic defects into angles and ascending rami.

DISCUSSION

The vascular system[9] of the head and neck begins as a stage of endothelial lakes. These vascular lakes then coalesce into capillary channels, some of which develop a muscular envelope histologically resembling veins. This is designated as the retiform stage, which precedes the final differentiation into mature arteries and veins. One of the most widely accepted theories of development of congenital vascular lesions is an aberration of the natural progression to the stage of gross differentiation.[9] Arrest of maturation within the endothelial stage will produce capillary or cavernous hemangiomata. Failure of vascular development to proceed beyond the retiform stage produces mixed hemangiomata or arteriovenous (AV) fistulae.

Approximately 50% of congenital AV fistulae occur in the head and neck region.[10] It is interesting and clinically relevant to differentiate congenital from acquired AV fistulae.[10] The congenital fistula has multiple and diffuse anastomoses with the surrounding vascular network, in contrast to the discrete, limited number of connections to surrounding normal vessels identified in the traumatic fistula. It is theorized that because of a gradual onset and progression, the congenital AVM is usually not associated with an enlarged heart and high output failure. Similarly, a positive Branham's sign (decrease in pulse rate and rise in blood pressure with compression of arterial supply to the AVM) is rarely seen in congenital cervical AVM, while common with the traumatic fistula.[11,12]

The childhood hemangioma is a vascular lesion that is present at birth approximately 40% of the time and proliferates during the first 3 to 6 months of life.[10] The female-to-male ratio is 5:1, and characteristically the lesion begins to involute at 1 year of age, completing spontaneous regression to a stable level by age 5 or 6. The AVM is nearly always present at birth, grows with the child, and does not regress with age. Congenital hemangioma is not generally found in the mandible. In contrast, the hemorrhagic mandibular lesion usually evolves from a congenital AVM.[10]

The hemodynamics of AV fistulae[10,13] can be simplified to represent blood flow from the arterial system directly into the venous complex, bypassing the high-resistance capillary bed. The large differential between the low-resistance AV fistula bed and normal capillary circulation continues to favor flow through the fistula. The continued flow distends the venous system distal to the fistula and thickens the tortuous vessel walls. Tissues adjacent to the AVM are relatively ischemic, since the high-resistance capillary bed has its blood supply shunted preferentially into the fistula. This tissue ischemia may be responsible for angiostimulation, proliferation of microfistulae, and later recurrence of hemodynamically significant larger fistulae.[10] It has long been contended that macrofistulae and microfistulae coexist, but the latter cannot be demonstrated angiographically. With insufficient resection of the primary malformation or after simple feeder vessel ligation, flow is rediverted by pressure differential into these potential fistulae, setting the stage for possible later recurrence.

The embryologic development of the internal and external carotid arteries may provide clues to the problem of recurrent AV fistulization.[9] The internal carotid artery derives from the dorsal aorta, while the external carotid arises from the ventral aorta. Connections between the two systems persist through

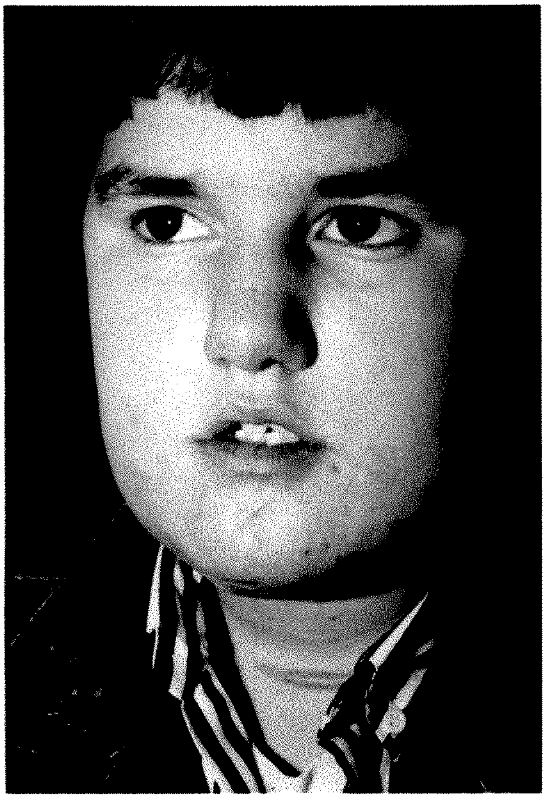

Fig 5. (Case 1) Six months after median labiotomy. Note mottling and ecchymosis of soft tissues secondary to persistent cavernous hemangioma.

the branchial arches. The middle meningeal artery, as a second-arch derivative, connects the intracranial and extracranial carotid systems. The ophthalmic artery, through the anterior and posterior ethmoid vessels, serves as another anastomotic link of the two systems. Additionally, the occipital branch of the external carotid artery joins the vertebral artery through its muscular branches in the suboccipital region.[14]

Before considering the clinical features of mandibular AVM, it is helpful to understand its frequency and distribution. Although the age of presentation[15] has been documented at both 3 months and 74 years, most lesions are diagnosed during the second decade. There is a 2:1 female-to-male ratio and lesions are twice as common in the mandible as the maxilla. The lesions may manifest symptoms during pregnancy, probably because of the high state of cardiac output and conversion of microfistulae to macrofistulae.[9,13,16] Combined maxillary and mandibular lesions do occur.

The most common symptom is spontaneous oral bleeding, and on inspection the hemorrhage may be seen to be under considerable pressure from around the necks of the teeth.[2,4] Involved molars (most commonly first and second) may be displaced and hypermobile from root absorption. On digital pressure, the tooth structure may feel as if it rests on a spongy bed rather than a rigid osseous framework. Pain, throbbing, and a sensation of pressure have all been described. Patients may demonstrate dysesthesia of the lower lip and chin in conjunction with an expansile mass compressing the inferior alveolar nerve. The adjacent skin and mucosa may be discolored from hypervascularity and frequently show dilated veins or frank vascular nevus formation.

A major aim of this discussion is to alert the clinician to the existence of this lesion before hemorrhage has become manifest. This level of awareness will avoid the cascading consequences of biopsy or tooth extraction. Simpler clinical maneuvers can clinch the diagnosis and dictate the need to perform angiography and adjunctive imaging studies. Palpation of the molar dentition and mandibular cortex will often demonstrate a spongelike compressible defect.[17] Auscultation of the mandible and adjacent external carotid arterial branches will usually reveal a prominent bruit. Some authors have advocated needle aspiration, with frank blood recovery under pressure being virtually diagnostic.[18]

Conventional mandibular radiographs[3,19] and pantomography (Panorex) may also lend suspicion to the presence of an AVM. The lesion is usually seen as an osteolytic defect with an altered trabecular pattern, thinned in some areas and thickened in others. A multilocular "soap bubble" appearance is most often encountered, although the less common presentation of bony spicules extending at right angles into the lesion (sunburst or sunray pattern) is highly diagnostic of AVM.[3,19] Teeth are usually displaced and root absorption is common. Occasionally, the inferior alveolar canal is widened[18] or the entire central marrow cavity replaced by the malformation (Fig 6A).

The patient will often require transfer to a hospital after massive bleeding from dental extraction, or present with lesser-magnitude spontaneous sentinel bleeding if no manipulation has preceded it. In these circumstances, arteriography is the obvious next maneuver and will reveal the nature of the disorder. The magnitude of the lesion is frequently underestimated by the angiographic study.[18,19] Bilateral four-vessel angiography should be performed to document the precise supplying vasculature and serve as a comparison should recurrence follow therapeutic efforts at eliminating the malformation. Besides adding information concerning the local mandibular lesion, angiography is important in elucidating the coexistence of maxillary involvement. Finally, superselective techniques lend themselves to therapeutic embolization of afferent vessels.

In occasional drastic circumstances, it may be prudent to initiate embolization at the time of initial angiography. However, a very careful, well-designed management scheme, to include preoperative embolization followed by surgical extirpation, will often necessitate delaying embolization until

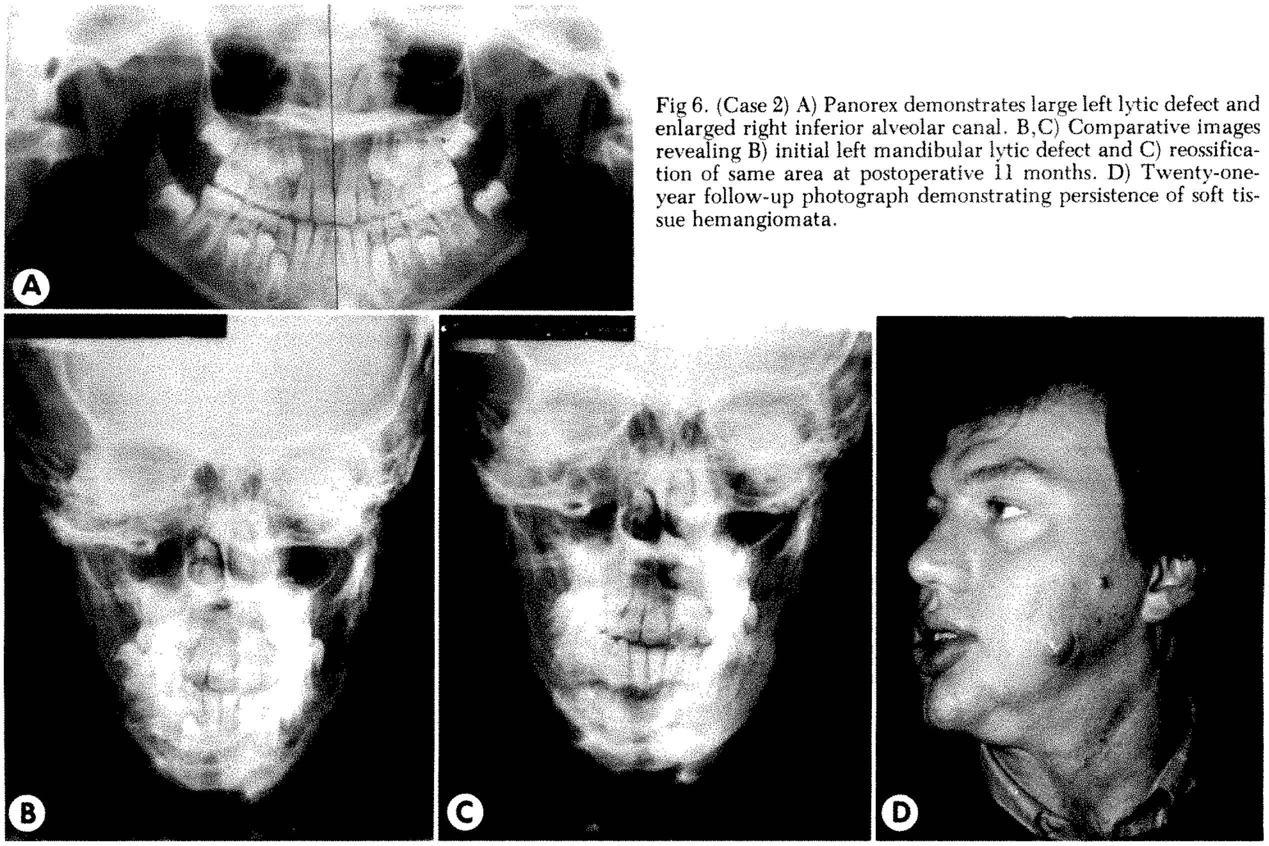

Fig 6. (Case 2) A) Panorex demonstrates large left lytic defect and enlarged right inferior alveolar canal. B,C) Comparative images revealing B) initial left mandibular lytic defect and C) reossification of same area at postoperative 11 months. D) Twenty-one-year follow-up photograph demonstrating persistence of soft tissue hemangiomata.

all diagnostic studies have been completed. For instance, CT scanning[10] has proven to be invaluable in delivering adjunctive information in bilateral lesions, drastically altering surgical planning. Flow through multiple afferent cortical vessels may be so expansive that embolization techniques have no effect on the lesion's hemodynamics. When embolization is employed, Gelfoam appears to be the preferred agent, although oxidized cellulose, polyvinyl alcohol, methyl methacrylate, silicone spheres, and isobutyl 2-cyano acrylate have their advocates.[12,20] Complications of embolization do occur even in the best of hands and include stroke, blindness, skin sloughing, and cranial nerve palsies.[10] A case of tongue tip necrosis in embolization of a mandibular AVM has been described.[21]

The management of a mandibular AVM has many facets, but its logical starting position is with the emergency situation. Weisberger[4] succinctly and accurately emphasized a high level of intensity when confronting one of these lesions as he stated, "For the first time in my life, I have been terrified in the operating room." Any physician or dentist who has faced an oral cavity hemorrhage of AVM magnitude can clearly empathize with this statement. In order to avert the unplanned irreversible hemorrhage, a hands-off, orderly approach to the initial problem is warranted. Although aspiration has been emphasized as a helpful adjunctive technique, there are cautions and problems even with this simple manipulation.[17,18] Certainly, open biopsy and dental extraction are to be avoided at nearly all costs, even in the controlled setting of the operating room. Each AVM has a different size, location, and blood supply, which dictate different management techniques. In order to profile the variations in therapy, three separate basic situations should be examined: 1) unilateral mandibular AVM, 2) bilateral mandibular AVM, and 3) combined mandibular and maxillary AVM.

UNILATERAL MANDIBULAR ARTERIOVENOUS MALFORMATION

The most common presentation is the unilateral lesion in the vicinity of the first and second molars. As an initial emergency measure to control major hemorrhage, multiple selective vessel ligation may be required. Although tempting as a conservative measure, simple ligation alone is ineffective in long-term control of the AVM and may be harmful.[4,7,22,23] One case report[24] in which external carotid artery ligation alone was successful with radiographic confirmation of osseous regeneration at 2½ years is anomalous and clearly at variance with most published reports and observations. Simple vessel ligation stimulates collateral blood supply and creation of new macrofistulae. In addition, ligation of the external carotid artery precludes the use of subsequent conventional angiography.[23]

Sclerosing solutions such as sodium morrhuate, sodium tetradecyl sulfate, and absolute alcohol have been used with unpredictable results.[12,24] Radiotherapy has enjoyed sporadic success, but is rarely employed as definitive management.[14] Embolization and subsequent dental extraction within a few days has been recommended in a series of three cases.[21] However, one of the three patients experienced subsequent severe hemorrhage and cardiac arrest, reflecting an inadequate basic management scheme.

Most individual case reports and published series demonstrate the logic in definitive resection of the basic pathologic lesion and microfistulae to avert revascularization of the malformation.[3,4,5,10,14,15,17,18,22,25,26] Some form of embolization and vascular obliteration is recommended hours or days in advance or even concurrently under the same general anesthesia in the operating room. Biller et al[26] have used an intraoperative technique under fluoroscopic control. They proceed with ligation of the feeding vessels, proximal ligation of the external carotid artery to avoid reflux of embolic material into the internal carotid circulation, and embolization after distal catheterization. Definitive resection of the fistula may be accomplished in several innovative ways after temporary devascularization. In spite of embolization or ischemic techniques, considerable intraoperative bleeding is usually encountered.

Reduction of blood pressure through reverse Trendelenburg positional change and pharmacologic agents such as sodium nitroprusside are helpful adjunctive techniques.[22] Creation of a buccal plate window and curettage of the lesion with gauze packing of the defect has often been definitively successful.[5,17,25] Others have tried resection of the hemimandible to a position anterior to the radiographic extent of the lesion, curettage of the interior of the mandibular segment removed, and rewiring of the segment in position with protracted internal maxillary fixation.[19,27] Complete resection of the mandibular segment, even to the point of hemimandibulectomy,[15,22] has been necessary in uncontrollable lesions. Tray mandibular reconstruction with cancellous bone has been employed at the time of definitive resection and as a delayed technique. Complications of infection and extruding sequestrae have been bothersome but not insurmountable, occasionally requiring complete removal of the apparatus and delayed revision.[3,18]

BILATERAL MANDIBULAR ARTERIOVENOUS MALFORMATION

The bilateral AVM is a considerably more challenging problem because of the larger size of the actual lesion, the greater number of major feeding vessels; the inability to devascularize the process with unilateral, preoperative embolization techniques; and the unacceptability of the option of near-complete mandibulectomy. The case report by Lamberg et al[1] in which delayed exsanguinating hemorrhage occurred from the opposite side reinforces the need to approach the entire lesion in a definitive rather than expectant manner. In fact, it was this single case that prompted our resolve to deal with the contralateral lesion in case 1, in spite of the fact that hemorrhaging was under control. In the context of case 1, several important management principles evolved in working through the technical problem. Angiography was helpful but somewhat inaccurate in defining the feeding vasculature. Vessels measuring 3 to 4 mm entering through the buccal mandibular plate were somewhat obscured by the overlying angiomatous vessels of the involved soft tissues of the cheek and lip. Attempts at embolization were ineffective because of the massive flow through the lesion and extensive collaterals.

The CT scan following the initial procedure proved invaluable in defining an optimum treatment protocol. The scan demonstrated that the lesion extended contiguously to the opposite side internal to the symphysis, and it retrospectively confirmed numerous defects in a cortical plate through which collateral vessels perforated to the malformation.

During operation on the contralateral mandible, the use of the "cell saver" assisted greatly in avoiding dilution of clotting factors and maintenance of proper volume status (John Conley, personal communication, 1986). The issue of working with the cell saver in a contaminated environment proved to be little more than a theoretic problem. The lip-splitting incision provided much greater visualization and potential for control of the large, weak-walled afferent vessels through the cortical plates. These vessels are so fragile that only bone wax techniques can control the dramatic loss of blood.

Intraoperative selective ligation of all afferent and efferent vessels was required in order to adequately devascularize the mandible prior to definitive resection. The mandibular arterial supply[7,28] derived principally from the internal maxillary artery with additional contributions from the facial and lingual vessels. The inferior alveolar artery descends from the maxillary artery as the latter passes forward between the ramus of the mandible and the sphenomandibular ligament. Within the mandibular canal, the inferior alveolar artery gives off the mental branch, which leaves the foramen to anastomose with the submental and inferior labial branches of the facial artery. The incisor branch continues forward within the mandible to anastomose with its mate of the opposite side. It is likely that this branch establishes the platform for intramandibular development of the bilateral lesion. Additional collaterals of the inferior alveolar artery to the lingual artery and the myelohyoid muscle provide potential alternate vascular networking. Thus, ligation of the lingual vessels, inferior alveolar vessels distal to the myelohyoid takeoff, facial vessels, and all anomalous macrofistulous vessels is required to reduce the pressure head to the AVM.

Finally, cortical buccal windows, curettage of the entire interior of the bilateral mandibular defect, and obliteration with cancellous bone and fat prevented redevelopment of the AVM in a potential osseous void. In addition, the bone grafts were placed to accelerate reossification and to strengthen this virtually hollow mandible.

COMBINED MANDIBULAR-MAXILLARY ARTERIOVENOUS MALFORMATION

The combined mandibular-maxillary AVM[14,29] may be the greatest challenge of all. The maxillary AVM has a great potential collateral supply from both vertebral and internal carotid systems[14] that reduces the capability of embolization techniques. Ligation of vessels alone is contraindicated, since anastomotic vessels can develop bilaterally and initiate reversal of flow with steal capabilities.[14] Maxillectomy may be required as definitive attempts at management are dictated by bleeding episodes. A report of consumption coagulopathy in extensive combined-area lesions has been described, requiring the use of heparin adjunctive to management of the bleeding[29] — a heroic task in this highly vascular problem. In its most severe form, a combined lesion may require cardiopulmonary bypass and deep hypothermic arrest.[29] Most of these combined lesions have overlying soft tissue angiomata, as in case 2, and patients often develop intermittent lesser bleeds after initial definitive resection of the primary AVM. The 21-year follow-up is believed to be the longest described in the literature and profiles the lifelong frustration that these patients experience with intermittent bleeding. Subsequent episodes have been brief and of limited magnitude in both presented patients, usually arising from the soft tissue rather than dentoalveolar components.

In summary, the management of bilateral concurrent or sequential AVM of the mandible is discussed in the framework of the lesser unilateral lesion. The otolaryngologist–head and neck surgeon has infrequent exposure to this problem and may be called upon in emergency settings to provide definitive care. The significance of sentinel molar bleeding cannot be overemphasized, and it is hoped that this report and others like it will shed new light on appropriate diagnostic and management techniques. The symptoms of these lesions may span decades. In order to deal with complications or new vascular lesions, the basic pathophysiology and anatomy must be digested. In the course of managing these two cases, the authors have identified a few helpful techniques, which are outlined as follow: 1) CT scan as an adjunct to arteriography, 2) the use of the cell saver, 3) the lip-splitting incision for better exposure, and 4) curettage and adipose-cancellous bone obliteration after selective vascular ligation.

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Ann Otol Rhinol Laryngol 100:1991

MASSIVE OROFACIAL ABSCESSES OF DENTAL ORIGIN

LOUIS W. WELSH, MD
JOHN J. WELSH, MD
JOHN J. KELLY, MD
JENKINTOWN, PENNSYLVANIA

Massive cervicofacial abscesses of dental origin are relatively rare, and may be associated with serious and grave morbidity. In extreme cases, an occasional fatality may result from regional complications. Three cases are presented that describe the clinical and radiographic evaluation and the surgical approaches for abscess drainage. Specific attention is directed toward 1) the management of imminent airway obstruction, 2) the application of computed tomographic technology for localization and surgical planning, and 3) current antibiotic therapy.

KEY WORDS — dental abscess, orofacial abscess.

INTRODUCTION

Massive craniofacial infections of dental origin are relatively uncommon and may be associated with serious morbidity and, rarely, fatal complications. The most emergent problem in the management of these cases is acute airway obstruction. Regional problems can include local tissue destruction, vascular occlusion, cranial nerve disruption, bacteremia, septic abscess, and intrathoracic extension. Three cases are presented that illustrate the varieties of onset and many of the major problems consequent to massive infections arising from dental sources.

From an overview of these clinical problems, the authors suggest a management program based upon the clinical presentation, radiographic data, maintenance of the airway, and appropriate antibiotic therapy.

A mixture of organisms may be cultured from orofacial abscesses of dental origin, usually three or four agents per case. The initial agent is aerobic[1-3] and is subsequently followed by a preponderance of anaerobic bacteria.

The classification of the fascial planes and spaces within the the cervical region proposed by Levitt[4] provides the anatomic foundation for this discussion. This scheme, a composite of numerous anatomists and clinicians,[5-8] recognizes the relationship of the compartments to the vascular, neural, and visceral components of the neck and potential continuity into the mediastinum. The fundamental concepts of lateral and central compartments and the horizontal division by the hyoid bone into superior and inferior regions have clinical and surgical significance. The mode of spread from one compartment to an adjacent space is by dissolution of the intervening fascial sheets and/or focal destruction of the muscle boundary. Accordingly, a dental abscess may originate in the juxtamandibular or maxillary region, spread to the adjacent pterygomandibular or masticator space, and thereafter from these areas extend rapidly to the base of the skull superiorly or laterally into the temporal space. Inferior dissection via the retropharyngeal and visceral vascular spaces may involve the mediastinum by direct continuity.

The surgical approach is contingent upon the location of the abscess, which is identified clinically and reinforced by an appropriate radiographic examination. The procedure itself must be timely to prevent the spread of infection and the consequences of regional destruction, as well as adequate in scope to evacuate and decompress the abscess against further loculation and delayed recurrence.

CASE REPORTS

Case 1. A 22-year-old man was admitted for management of facial pain and swelling extending from the angle of the mandible to the supratemporal fossa. The patient had undergone extraction of the right mandibular third molar 7 days prior to the examination; thereafter facial and cervical swelling increased dramatically in spite of broad-spectrum antibiotic therapy.

On examination, the patient appeared toxic and febrile (39°C), trismus was severe, and the oral airway was compromised. Firm induration over the lateral skull, the ascending ramus of the mandible, and the malar bone was noted.

A computed tomography (CT) scan of the head taken prior to operation revealed the extent of the abscess, with invasion of the parotid area and retromandibular compartment and extension into the pterygoid region (Fig 1A). Cranial views above the orbital level revealed a massive subcutaneous abscess without evidence of bone destruction (Fig 1B).

The patient underwent an incision and drainage

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REPRINTS — Louis W. Welsh, MD, 179 Washington Lane, Jenkintown, PA 19046.

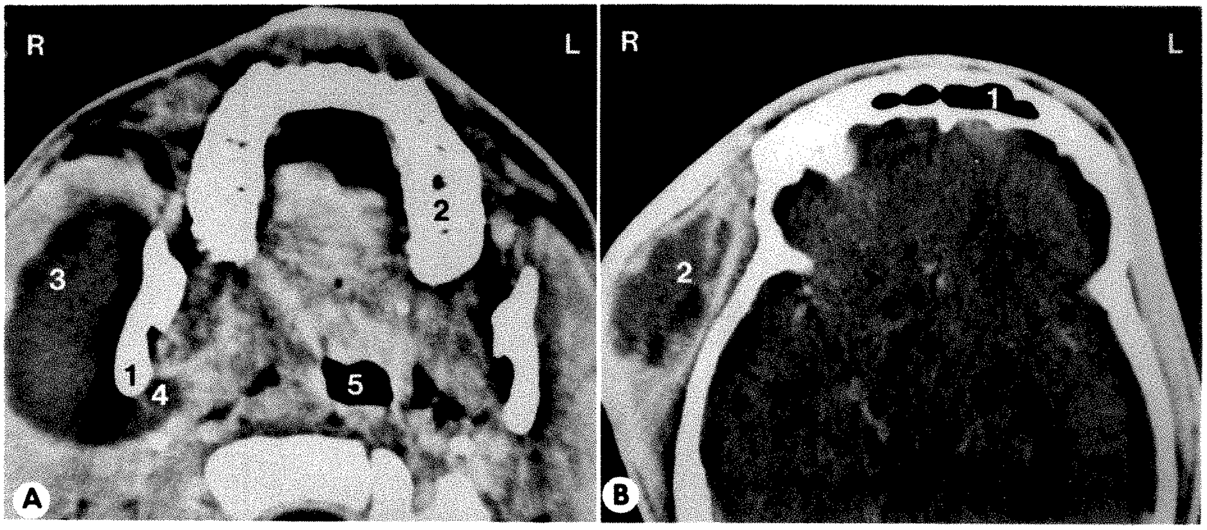

Fig 1. (Case 1) Horizontal computed tomographs. A) Of condyle. 1 — subcondylar level, 2 — maxillary alveolus, 3 — 6 x 4-cm abscess, 4 — retromandibular extension into masseter space, 5 — soft tissue compression of nasopharyngeal airway. B) Of frontal sinus. 1 — frontal sinus level, 2 — 4 x 5-cm abscess in temporal space.

of the pterygomandibular space abscess through a submandibular approach, evacuating approximately 60 mL of purulent material. A second approach through the temporalis fascia into the supratemporal fossa released 50 mL of additional foul-smelling pus.

The bacterial cultures identified *Streptococcus intermedius* with broad sensitivities, *Staphylococcus epidermidis* resistant to penicillin, and *Bacteroides* species by Gram stain. The postoperative course was protracted; purulent drainage ensued for approximately 10 days thereafter. Finally the patient was discharged, with continued edema and induration of the parotid region, on a prolonged antibiotic regimen. The recovery was complete when he was last examined, 3 months following the dental extraction.

Case 2. A 65-year-old man was admitted through the emergency room for severe airway obstruction and facial swelling. He had previously undergone multiple dental extractions 1 week earlier for extensive carious disease. Owing to increasing swelling in the submandibular region 3 days postoperatively, antibiotics had been prescribed, but apparently they made little impact upon the general progression of the inflammatory process. On clinical examination, the man was obese, severely dyspneic, and massively swollen over the right side of the face and neck.

Lateral soft tissue radiographs of the neck demonstrated a retropharyngeal collection extending along the cervical spine from C-1 to C-6 and a large abscess at the angle of the mandible (Fig 2A). The supraglottic structures were markedly distorted by edema.

Owing to severe trismus that precluded oral intubation, he was intubated transnasally with bronchoscopic assistance. Multiple drain sites were established in the pterygomandibular, masseter, retropharyngeal, and vascular spaces (Fig 2B). The bacterial smear identified several pathogens, aerobic and anaerobic, including gram-positive cocci and gram-negative bacilli. Final cultures revealed *Streptococcus* group F and mixed skin flora. Four days postoperatively, abscesses appeared in the left side of the neck, parotid region, and cheek that required multiple secondary drainage approaches. The antibiotic program was modified according to the newly identified bacterial sensitivities.

Case 3. A 28-year-old man was transferred for management of a temporal lobe abscess and extensive facial infections (Fig 3A). Five weeks earlier a left maxillary third molar had been extracted; 3 days later an abscess was drained via a submandibular incision. Several days thereafter, personality changes and progressive stupor were observed. A CT scan demonstrated a temporal lobe abscess (Fig 3B) that was followed by cranial trephine and aspiration, revealing mixed flora including *Streptococcus* group F, *Bacteroides uniformis*, *Peptostreptococcus*, and *Staphylococcus epidermidis*. The intracerebral abscess was monitored by periodic CT and required two additional aspirations before final resolution. Cultures from the facial abscess included *Streptococcus* group F and *Streptococcus viridans*. In spite of apparently appropriate antibiotic and surgical therapies, an abscess of the extracranial temporal fossa appeared 10 days later, requiring further surgical drainage. Progression of the disease to an osteomyelitis of the ascending ramus (Fig 3C) and mandibular condyle eventuated in osteolytic destruction of these structures. Gradual control of the infection was achieved by removal of the destroyed mandibular segment, wide drainage of the abscess cavity, and prolonged antibiotic therapy.

After several months of intensive therapy, the patient was discharged from the hospital on continued

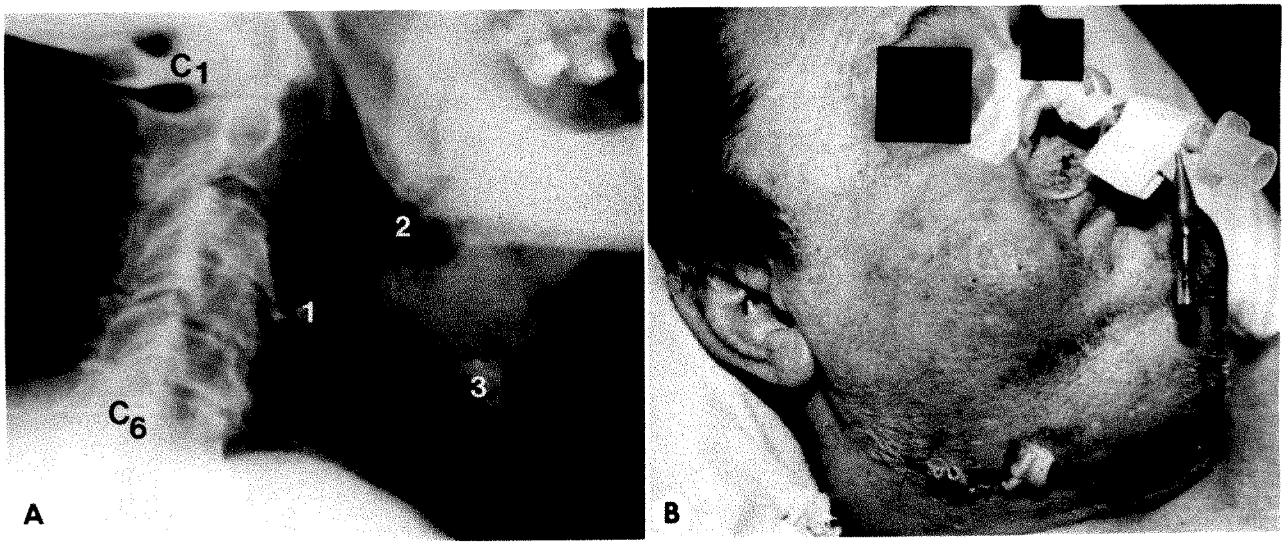

Fig 2. (Case 2) A) Lateral view of cervical region. 1 — retropharyngeal collection from C-1 to C-6, 2 — abscess at angle of mandible, 3 — edema of supraglottic larynx. B) Patient with airway maintained by endotracheal intubation and incision with drains in submandibular, retropharyngeal, and lateral pharyngeal spaces.

antibiotic therapy. Six months later he underwent prosthetic reconstruction of the mandibular defect with satisfactory functional recovery.

On the sixth postoperative day, the patient developed a left subclavian vein occlusion. Finally, tracheotomy was necessary at 8 days to alleviate the laryngeal obstruction. The subsequent course was complicated by prolonged drainage from the drainage sites and gradual recanalization of the occluded vein. After 4 weeks of aggressive antibiotic therapy, he was discharged from the hospital in satisfactory condition.

THERAPEUTIC PROGRAM

The comprehensive approach to the management of cervicofacial abscesses is predicated upon five areas.

1. Evaluation of airway patency and alleviation of obstruction by intubation or tracheotomy (the immediate consideration).
2. Radiographic investigation, if necessary, to determine the state and extension of the inflammatory process (second priority).
3. Drainage of the phlegmon to interrupt the progression of local destruction (third level of concern).
4. Appropriate and specific antibiotic therapy contingent upon aerobic and anaerobic cultures (supportive program).
5. Delayed reconstruction and/or immediate repair as needed.

We shall not discuss the surgical aspects of the problem, since there are numerous references that comprehensively present the techniques required for the interested clinician. However, the issues of airway maintenance, the current standard radiographic studies, CT investigation, and the selection of antibiotic therapy will be discussed in relation to the presented cases.

Airway Protection. Pharyngeal wall edema may encroach upon the supraglottis, rapidly narrowing the lumen until total airway obstruction ensues. In the extreme situation, examination of the larynx can be potentially perilous, akin to that of infantile acute epiglottitis, revealing retention of secretions and brawny induration of the epiglottis, ventricular bands, and aryepiglottic folds spilling over into the postcricoid region. Of interest, the subglottic and tracheal regions appear unaffected by the adjacent inflammatory response. We observe that abscesses at or above the level of the vocal cords are more likely to cause laryngeal obstruction than the inferiorly located disorders caused by hypopharyngeal or esophageal perforation. The approaches to airway maintenance are 1) direct peroral laryngeal intubation, which must be approached in the erect position to prevent positional collapse by obstruction of the epiglottis while the patient is in the supine position, 2) bronchoscopically assisted nasal or oral intubation, again in the upright position, with recognition that the normal anatomic landmarks may be grossly distorted, and 3) possible tracheotomy, although the procedure is technically difficult in the short-necked individual and compounded by regional inflammatory response.

The authors have employed each approach and suggest direct or fiberoptically controlled intubation in the most grave atmosphere, and tracheotomy when time permits. Again, as in the other critical areas, the preference of procedure is based upon surgical experience and expertise. Controlled tracheotomy may be performed after laryngeal intubation.

Radiographic Investigations. Computed tomography provides comprehensive information with respect to 1) the location and extent of the inflammatory process,[9-11] 2) the state of infection, ie, cellulitis versus abscess formation,[12] 3) evaluation of areas

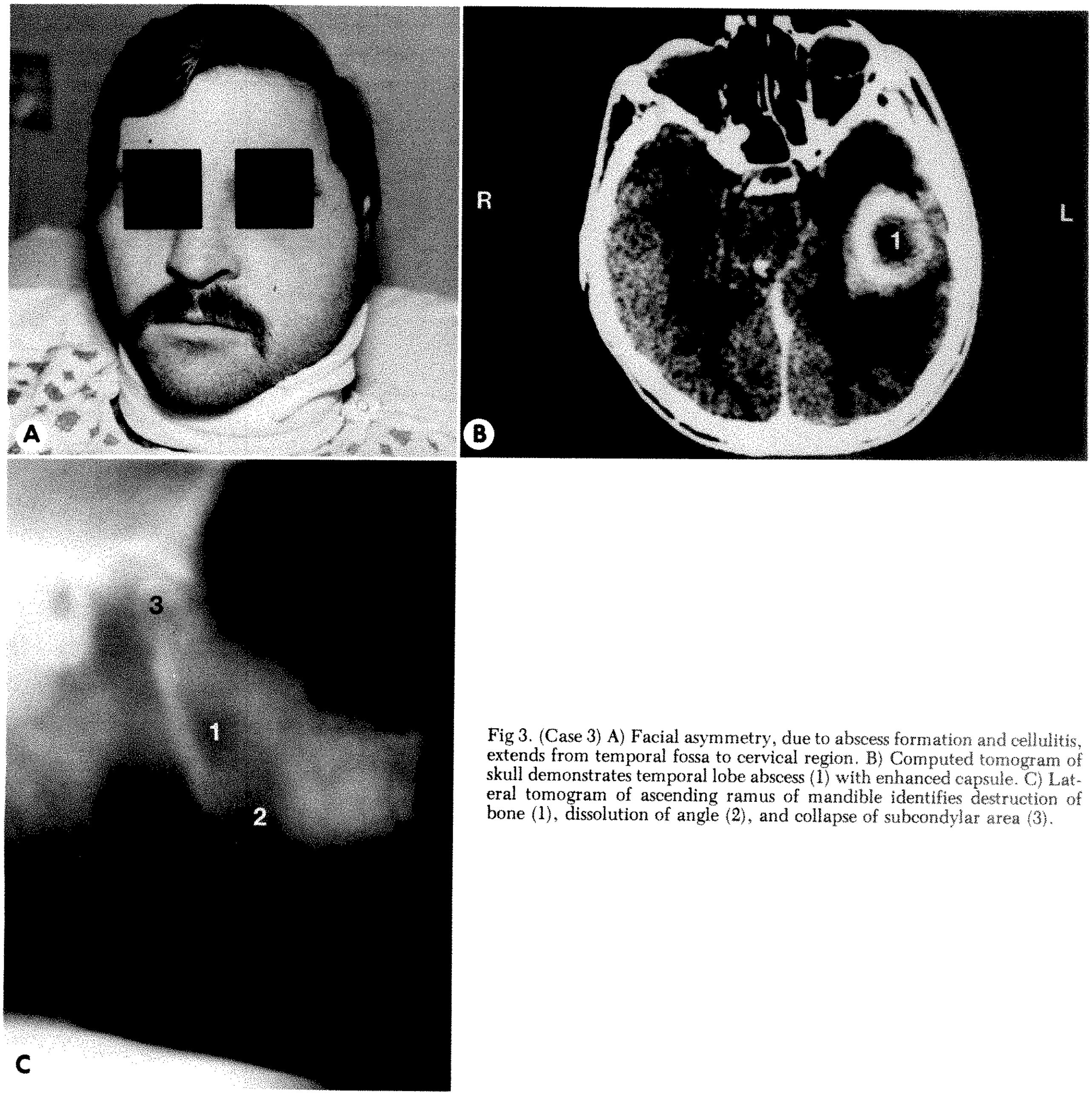

Fig 3. (Case 3) A) Facial asymmetry, due to abscess formation and cellulitis, extends from temporal fossa to cervical region. B) Computed tomogram of skull demonstrates temporal lobe abscess (1) with enhanced capsule. C) Lateral tomogram of ascending ramus of mandible identifies destruction of bone (1), dissolution of angle (2), and collapse of subcondylar area (3).

difficult to examine owing to location of the infection, ie, pterygoid area, and 4) clinical conditions that preclude adequate visualization, such as trismus.

Cellulitis is characterized on CT scan as a soft tissue swelling with obliteration of the adjacent fat planes. An abscess is identified as discrete, low-attenuation areas within a soft tissue inflammatory mass, and may be enhanced by contrast media.

Correlation between a CT scan identifying an abscess and surgical exploration is highly reliable. Holt et al[9] describe six cases with evidence of abscess by CT and positive surgical exploration in each instance. Nyberg et al,[12] via a series of 31 cases, identified one false positive by CT involving the submandibular, visceral, and vascular spaces, and a false negative involving five cervical spaces subsequent to dental extraction — an accuracy of 94%.

The application of CT in the evaluation of cases 1 and 3 precisely defined the extent of the infection and clarified the source of the neurologic deficit due to the intracerebral abscess. In these two cases definitive procedures could be programmed, in spite of the marked delay in initiating therapy. Case 2, in which soft tissue radiographs were taken, illustrates the evolution of the cellulitis to abscess formation and the need for continued clinical reevaluation and repeated radiographic survey.

Antibiotic Therapy. The constant development of new antibiotics with spectra accommodating the emerging resistance to current therapy, variations in optimal therapeutic regimens (ie, dosage and

POSSIBLE ANTIBIOTIC REGIMENS FOR TREATMENT OF OROFACIAL ABSCESSES

	Choice A	*Choice B*	*Choice C*
Anaerobes			
Bacteroides sp	CL	AM-SU	
Peptostreptococcus	P	CL	
Peptococcus	P	CL	
Fusobacterium sp	P	CL	CE
Clostridium sp	P	CL	CH
Aerobes			
Streptococcus	P	CE CL E	V
Enterobacter sp	CE	AM	
Pseudomonas aeruginosa	CE	PIP	T
Staphylococcus aureus	P or N	AM-CL	V

CL — clindamycin, AM-SU — amoxicillin-sulbactam, P — penicillin, CE — ceftazidime, CH — chloramphenicol, V — vancomycin, E — erythromycin, AM — aminoglycosides, PIP — piperacillin, T — ticarcillin, N — nafcillin, AM-CL — amoxicillin-clavulanate.

duration), and the individual preferences of medical microbiologists permit some degree of latitude in the choice of agents. Our plan, illustrated by the following scheme, suggests the primary agents that are effective and alternative choices when patient intolerance, susceptibility, and method of absorption demand a secondary medication. We shall consider only the more common bacterial groups, although other agents may occasionally be identified in these infections.

At the initial patient confrontation prior to obtaining of laboratory data, in view of the fact that the microbes are usually flora indigenous to the mouth, the therapeutic agent of choice is either clindamycin or a later-generation penicillin with a β-lactamase inhibitor such as amoxicillin-clavulanate (oral) or ampicillin-sulbactam (parenteral).

After laboratory data become available, the therapy of mixed anaerobic and aerobic agents may require multimodal agents, contingent upon identification and in vitro therapeutic responsiveness (see Table).

While penicillin historically has been the primary choice of therapy for head and neck infections, empiric therapy now requires a selection of agents that provide coverage for β-lactamase–producing organisms (eg, *Bacteroides oralis* or *Bacteroides melaninogenicus*).

Third-generation cephalosporins (eg, ceftriaxone) may be employed initially for the enteric gram-negative rods. Alternatively, the aminoglycosides or later generations of the penicillins may be selected, contingent upon tolerance and responsiveness to the agent.

The pathogenicity of *Pseudomonas* is well recognized, although fortunately this microbe is relatively uncommon in dental infection. Courses of ceftazidime or piperacillin, with or without an aminoglycoside, appear to be equally effective. Aminoglycosides may be considered in the therapeutic plan, but the risks of renal damage and potential ototoxicity need be considered in the benefit-damage analysis.

Staphylococcus aureus can be involved as a primary pathogen or secondary invader. Accordingly, penicillin may be selected when penicillinase tests are negative; and when they are positive, nafcillin, oxacillin, or a similar agent may be employed. Finally, methicillin resistance requires vancomycin, which at this time continues to be effective.

The *Enterobacter* species are somewhat less common and respond to the aminoglycosides. Secondary selection of the later-generation penicillins and cephalosporins may be considered if contraindications to gentamicin or tobramycin are identified.

The anaerobic bacteria will respond to penicillin primarily, with the exception of β-lactamase–producing *Bacteroides* species, for which clindamycin is the primary selection. The second-level agents include amoxicillin-clavulanate and ampicillin-sulbactam. There is not a sufficient body of experience to recommend metronidazole in the treatment of serious head and neck infections.

Multidrug therapy programs were initiated in the presented cases and modified on the basis of continuing sensitivity analysis. The combination of penicillin and clindamycin in substantial dosages adequately controlled the infection in case 1. In case 2, penicillin, clindamycin, and an aminoglycoside were initiated according to the bacterial sensitivities. In case 3, five bacterial agents were identified (three aerobic and two anaerobic); the therapeutic protocol included penicillin, clindamycin, and, for a brief period, metronidazole.

Finally, antibiotic administration should be continued over an extended period to eradicate residual subclinical foci of infection and preclude recrudescence of a regional abscess. Current information on antibiotic therapy is available.[13-20]

DISCUSSION

A small incidence of complications following dental extraction is probably inevitable because of the advanced stage of infection at the time of patient presentation, and in spite of adequate antibiotic prophylaxis and proper surgery. The goals in these instances are 1) contain the progression of the abscess, 2) control the adjacent tissue damage, and 3) minimize the risk to life.

The authors describe a broad variety of complications in the intracranial, pericranial, facial, and cervical areas due to delayed recognition, inadequate therapy, or patient indifference. In addition to these regional problems, but not discussed in this paper, are the complications of intrathoracic abscess due to extension within the retropharyngeal and lateral pharyngeal spaces.

In the preliminary investigation, the authors suggest radiographic examination of the difficult-to-evaluate deep cervical abscesses, since the extension and margins of the collection can be identified and appropriate surgical intervention can be defined preoperatively. We do not request these studies nor suggest that they are essential in the planning of superficial, lateral cervical, or peritonsillar infections, nor in Ludwig's angina.

Surgical drainage remains the mainstay of therapy for cervical and pericranial abscesses. In addition, a complementary antibiotic program is used for septicemia, regional osteomyelitis, and local cellulitis. We have observed in a number of instances that prolonged and total reliance upon antibiotic therapy to the exclusion of surgical evacuation contributes to further expansion of the purulent collection and additional destruction of the adjacent structures.

The state of antibiotic therapy is in a constant progression contingent upon new antimicrobial agents and the emergence of mutant or resistant forms. The current therapeutic scheme illustrates the agents available at this time, and allows considerable latitude of choice based upon personal preference. Future agents may be selected as in vitro sensitivities warrant.

Overall, prevention of the regional infection rather than surgical intervention is the overriding therapeutic principle. Antibiotic therapy may not eliminate the complications in an individual when the factors of coexistent advanced dental caries, preexisting periapical abscesses, and poor oral hygiene predispose to local sepsis. Nonetheless, appropriate broad-spectrum antibiotic therapy in sufficient dosage in conjunction with postoperative observation is essential in working toward eliminating these complications.

SUMMARY

1. The broad panoramas of cervical and facial abscesses secondary to dental infection are depicted in the presented cases.
2. The clinical evaluation of airway obstruction and therapeutic options are described.
3. The role and diagnostic values of current radiographic techniques are reviewed.
4. The necessity for prompt surgical evaluation and guidelines for appropriate antibiotic therapy are outlined.

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PRIMARY CULTURE OF CHINCHILLA MIDDLE EAR EPITHELIUM

AKIHIKO NAKAMURA, MD
OSAKA, JAPAN
DAVID J. LIM, MD
COLUMBUS, OHIO

THOMAS F. DEMARIA, PHD
COLUMBUS, OHIO
CLEMENS A. VAN BLITTERSWIJK, PHD
LEIDEN, THE NETHERLANDS

Chinchilla middle ear epithelium was successfully cultured in medium containing Dulbecco's modified Eagle's medium, Ham's F12 mixture, and fetal bovine serum. After 3 to 5 days, the explants produced outgrowths of primarily flat polygonal and ciliated cells that persisted for up to 10 days in culture. These cells in the outgrowth often formed a "dome" indicating the presence of functional polarization and fluid transportation capability. The ciliated cells were more frequently found near the explant, and were fewer in number in the area distant from the explant. This finding suggests that the ciliated cells in the outgrowth are migrated ciliated cells deriving from the explant. That secretory cells were not identified in the outgrowth indicated that the present culture technique did not support secretory activity. Using the present culture technique, we were able to maintain the explants and primary cultured cells for up to 14 days in a majority of cases; hence, these techniques appear to be applicable to a number of in vitro studies.

KEY WORDS — cell culture, chinchilla, middle ear epithelium.

INTRODUCTION

Considerable progress has been made in recent years in cell culture techniques that allow for the successful culture of respiratory epithelial cells in many different species.[1] Recently, the middle ear epithelium was successfully cultured from the rat.[2] A number of investigators also have attempted to culture the middle ear epithelium from different species such as guinea pigs,[3] gerbils,[4] and chinchillas.[5,6]

The availability of cultured middle ear epithelial cells provides a new avenue for research that is useful in characterizing bacterial and viral receptors, hormone receptors, cell-cell interaction, cell differentiation, cell transformation (metaplasia), and measurement of cell potential.

Because this laboratory has been involved with developing an animal model for otitis media using the chinchilla, we have attempted to develop a technique to culture the chinchilla middle ear epithelium and to characterize these cells by using light and electron microscopy.

MATERIALS AND METHODS

Animals. A total of 20 healthy adult chinchillas (body weight, 350 to 400 g) were used.

Culture Medium. The culture medium was essentially the same as that described by van Blitterswijk et al,[2] with minor modifications. Our culture medium consisted of a mixture of three parts Dulbecco's modified Eagle's medium (Gibco) and one part nutrient mixture F12 (Ham's F12, Gibco) supplemented with 5% fetal bovine serum (Whittaker MA Bioproducts), hydrocortisone (0.4 μg/mL, Sigma), isoproterenol (10^{-6} mol/L, Sigma), penicillin (100 U/mL), and streptomycin (100 μg/mL, Gibco). Because the low-calcium medium used by van Blitterswijk et al to inhibit fibroblast growth during serial culture of the rat epithelium did not favorably support the chinchilla middle ear epithelium, in the present experiment we used the standard medium described above.

Culture Technique. The chinchillas were placed under general anesthesia with halothane. Middle ear mucosa was aseptically removed from the superior tympanic bulla, the inferior tympanic bulla, and near the tympanic orifice of the eustachian tube. Next, under sterile conditions, each specimen was chopped into very fine pieces (1 mm^3) with a surgical scalpel. To minimize bacterial contamination, these chopped pieces were immersed in the culture medium with penicillin plus streptomycin for at least 1 hour at 4°C. Each of the 8 to 10 fragments were then placed on individual 35-mm tissue culture dish surfaces (Falcon) or in a 24-well tissue culture plate (Falcon) in a small volume of culture medium without an epidermal growth factor (EGF) and were incubated at 37°C in a humidified atmosphere of 10% carbon dioxide. The volume of the medium was up to 2 mL in the 35-mm tissue culture dish incubating for 2 to 4 days in the primary culture. Four days after starting the primary culture, when outgrowth was visible on the culture dish, 10 ng/mL EGF (Sigma) was added to the culture me-

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From the Otological Research Laboratories, The Ohio State University College of Medicine, Columbus, Ohio (Nakamura, DeMaria, Lim), and the Department of Otolaryngology, University of Leiden, Leiden, the Netherlands (van Blitterswijk). Dr Nakamura is currently in the Department of Otolaryngology, Kansai Medical School, Osaka, Japan. This study was supported in part by National Institutes of Health/National Institute on Deafness and Other Communication Disorders grant R01 DC00090 and in part by an International Rotary Fellowship to A.N. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of The Ohio State University.

REPRINTS — David J. Lim, MD, Otological Research Laboratories, 4331 University Hospitals Clinic, 456 W 10th Ave, Columbus, OH 43210.

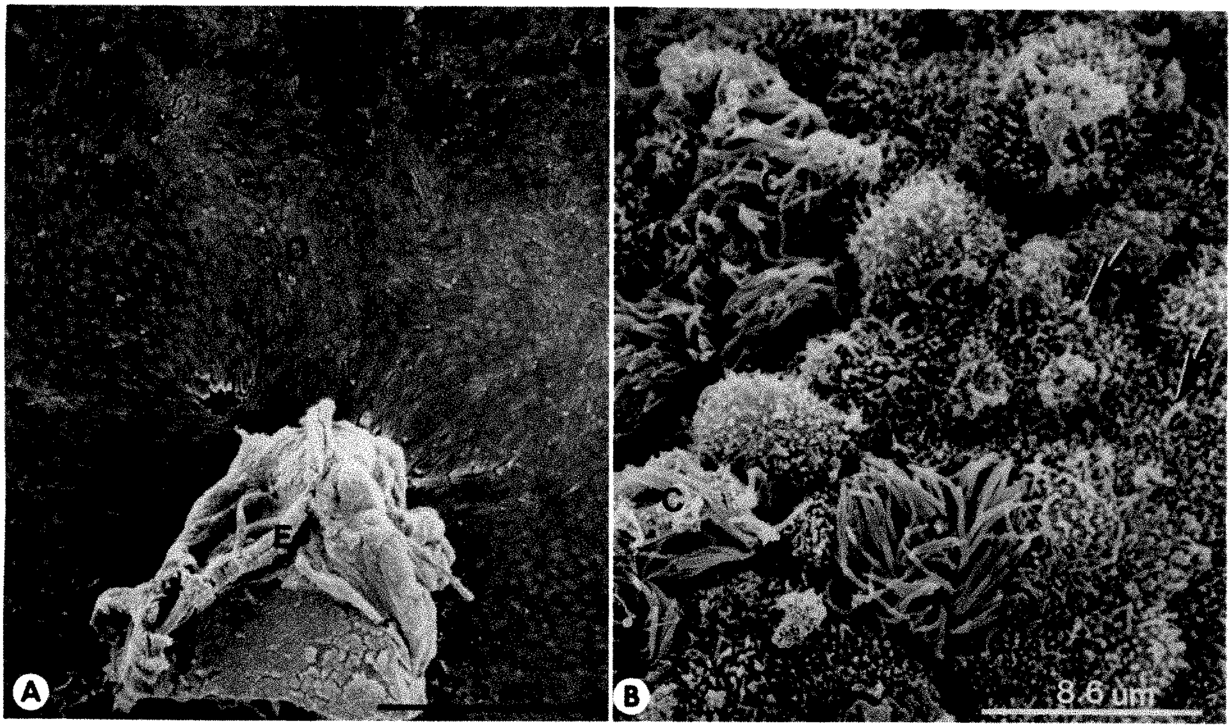

Fig 1. Scanning electron micrographs. A) Explant (E) and outgrowth (O) after 10 days in culture. B) Surface of explant, showing ciliated cells (C) and nonciliated cells with numerous microvilli of various lengths and densities after 10 days in culture. Several nonciliated cells possess primary cilia (arrows) on their cell surfaces.

dium. The medium was renewed twice a week.

Preparation for Morphologic Study. For the purpose of light microscopy, middle ear cells were cultured, examined with a microscope (Zeiss ICM 405), and photographed.

For electron microscopy, the cells were grown on the coverslip (Thermanox, Miles Scientific). For scanning electron microscopy (SEM), cells attached to the coverslip were rinsed free of culture medium with phosphate-buffered saline (PBS, 0.01 mol/L, pH 7.2) and fixed with 2.5% phosphate-buffered glutaraldehyde for the duration of 1 hour, followed by postfixation in 1% osmic acid in phosphate buffer and 2% tannic acid. Following graded dehydration with ethanol, the specimens were critical point dried with carbon dioxide. They were then sputter-coated with gold and examined by SEM (Hitachi S-570). For transmission electron microscopy (TEM), cells were cultured on the plastic coverslip. The specimens were fixed with 2.5% sodium cacodylate–buffered glutaraldehyde, thoroughly washed with a buffer solution, and postfixed in 0.33% osmic acid in S-collidine buffer for 1 hour. Next, they were dehydrated in graded alcohol and embedded in Epon. Finally, ultrathin sections were cut and double-stained with uranyl acetate and lead citrate, and examined by TEM (Philips 300).

Method of Examination. A total of 17 cultured cell strains obtained from different parts of the middle ear and grown on 35-mm tissue culture dishes were examined on the first day of outgrowth and on the 3rd, 4th, 5th, 7th, 10th, and 14th days after explant. The apical surface area of 100 cells chosen randomly from photographs of each cell line was measured by a digitizing system (Bioquant System IV). The number and distance of ciliated cell migration from the explant were counted and measured.

Histochemistry. Following diastase digestion and Alcian blue (AB) stain (pH 2.5), periodic acid–Schiff (PAS) stain was performed and those cells that stained positive were counted. We used four explants from the inferior bulla and four explants from the tympanic orifice of the eustachian tube for this study.

Statistical Analysis. A standard Student's *t* test was used for significance ($p < .05$).

RESULTS

Results demonstrating the influence of the explant removal time on the cell growth showed that the optimal time for removal of the explant was after 7 to 10 days (data not shown).

We obtained the most successful outgrowth of the epithelial cell from the inferior bulla near the eustachian tube by using the present cell culture method. Overall, the epithelial cell growth from the superior bulla was poor, as 32 of 40 explants (80%) from the inferior bulla and 35 of 40 explants (88%) from the tympanic orifice of the eustachian tube demonstrated outgrowth within 7 days of explantation. On the other hand, 9 of 40 explants (23%) from the superior bulla attached to the Petri dish and demon-

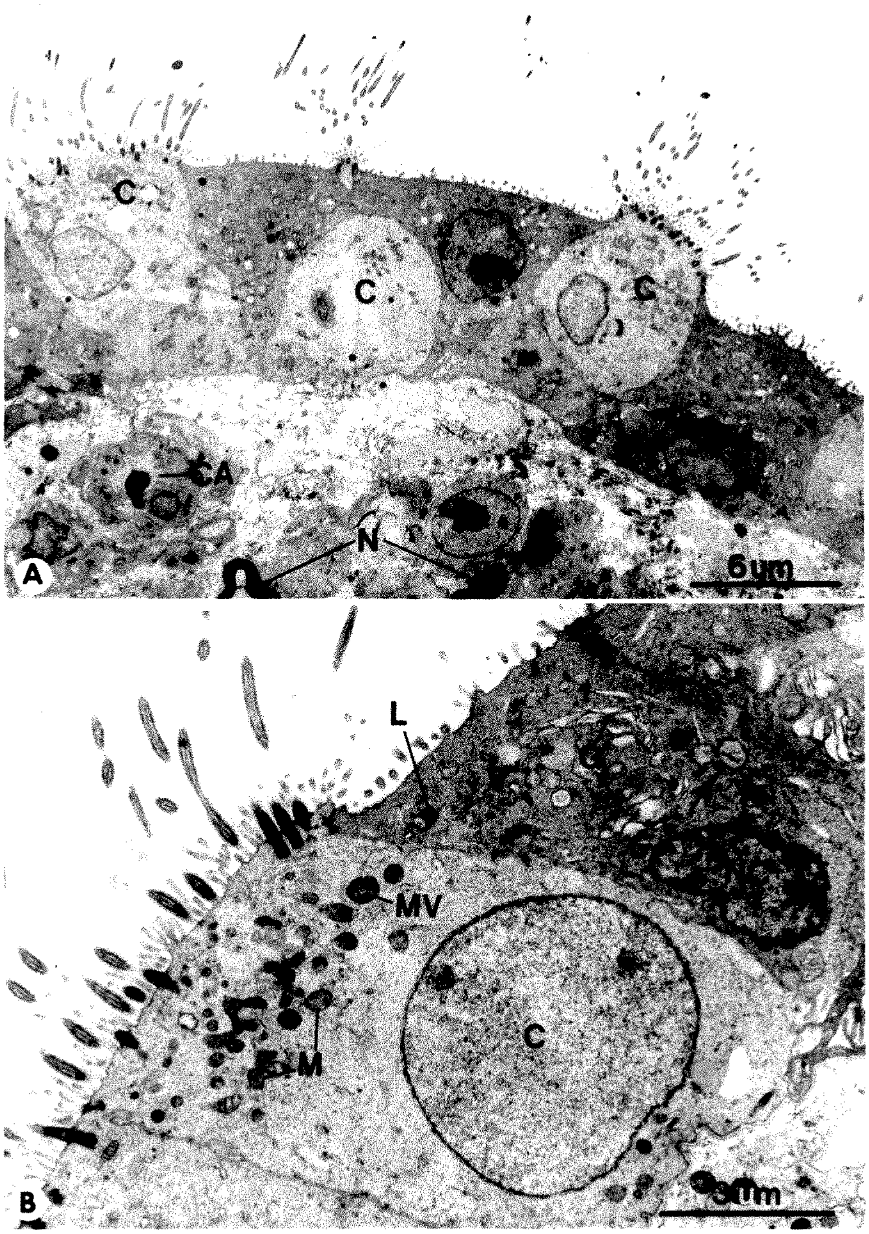

Fig 2. Transmission electron micrographs. A) Explant obtained from middle ear mucosa near tubal orifice after 4 days in culture, showing well-preserved ciliated (C) and nonciliated epithelial cells (original x1,200). CA — capillary, N — myelinated nerve fibers. B) Explant, showing well-preserved ciliated (C) and nonciliated cells (NC) after 2 days in culture. Ciliated cell is characterized by cluster of mitochrondria (M). Multivesicular body (MV) is also observed frequently. Nonciliated cell is characterized by dark cytoplasm due to heavy accumulation of ribosomes, by well-developed Golgi apparatus (G) and endoplasmic reticulum, and often by indented nucleus. Mitochondria are often swollen and enlarged (arrow) and appear exhausted. Some secretory granule-like structures (arrowhead) are observed, but they are difficult to discern from swollen small mitochondria. Osmiophilic lysosomal granules (L) are frequently seen.

strated outgrowth.

The 17 explants obtained from the inferior bulla or near the tympanal orifice of the eustachian tube demonstrated evidence of outgrowth by 3.1 ± 1.4 days (mean ± SD). In one cell line, outgrowth was found as late as the 8th day. When 6 to 7 explants of 10 were attached to 35-mm Petri dishes, cells became confluent or semiconfluent about 14 days after the start of primary culture.

Explant. The explanted middle ear epithelium (Fig 1A), which was cultured for up to 14 days, showed excellent morphologic characteristics, maintaining ciliated, nonciliated, and basal cells.

The SEM view of the surface of the explant clearly showed well-preserved ciliated and nonciliated cells with numerous microvilli, and few of these nonciliated cells possessed what appeared to be primary cilia by SEM observation (Fig 1B).

The TEM data showed excellent epithelial cell morphology with underlying connective tissue containing macrophages, capillaries, and nerve tissue (Fig 2A). The epithelial cells were cuboidal or columnar-shaped when the explants were obtained near the tubal orifice, or simple squamous when the explants were obtained from the bullar wall.

The ciliated cells contained numerous mitochondria in the apical part of the cell. There was distinct Golgi apparatus and lysosomal granules in the supranuclear region (Fig 2B).

The nonciliated cells were characterized by dark

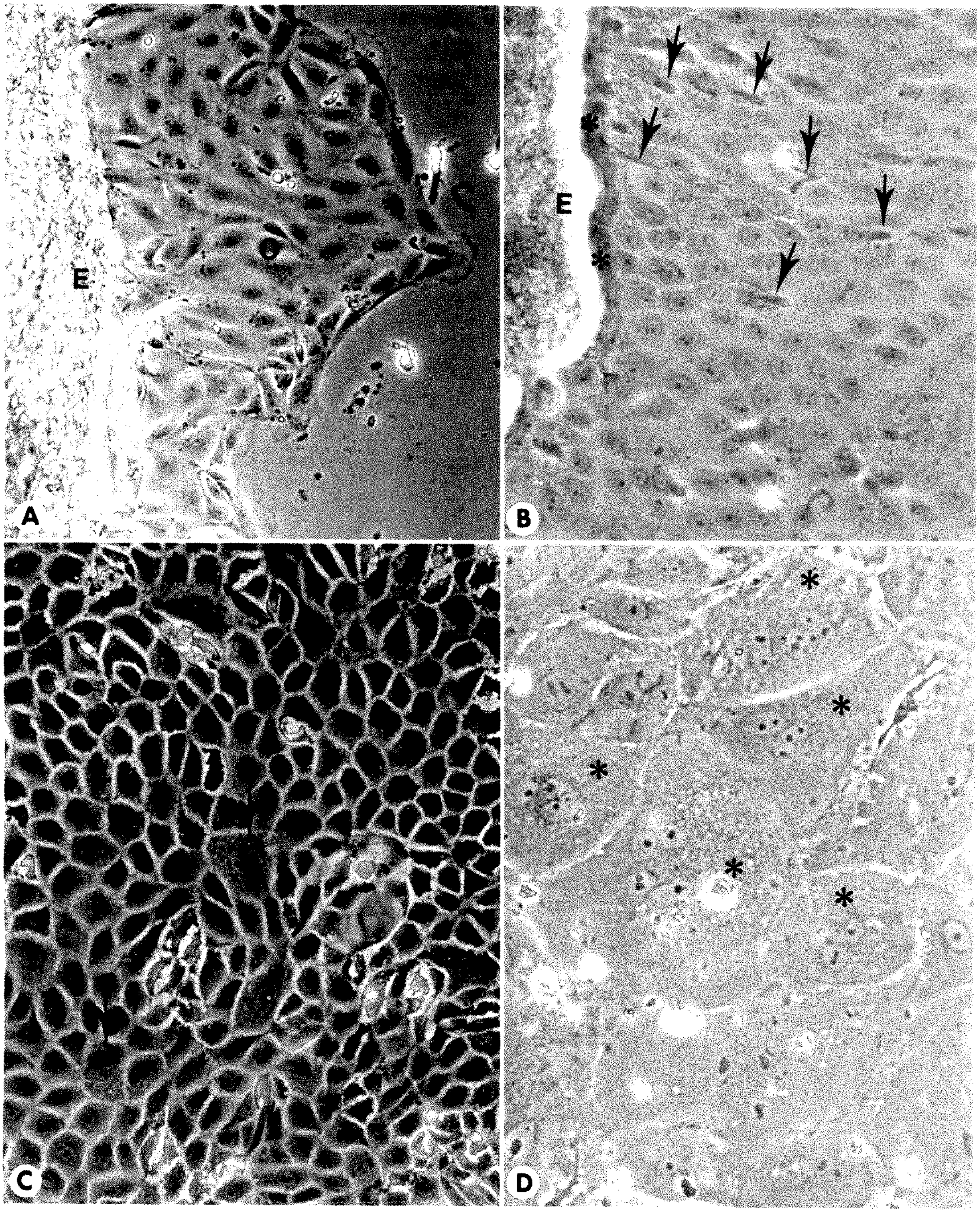

Fig 3. Light micrographs. A) Explant (E) and outgrowth (O) (original x300). B) Outgrowth after 10 days in culture, showing elongated migratory ciliated cells (arrows) and nonciliated hexagonal epithelial cells (original x400). Cilia of these cells in outgrowth are actively beating. Shady area (asterisks) along edge of explant (E) represents vigorously beating cilia. C) Outgrowth after 14 days in culture, showing typical cobblestone-appearing cells (original x200). Large cells that have two nuclei (arrows) appeared to be dividing. D) Outgrowth after 13 days in culture, showing giant cells with multiple nuclei (asterisks) (original x200). These cells may be transformed or dividing cells.

cytoplasm, owing to the large amount of ribosomes (Fig 2B). Also, well-developed rough endoplasmic reticula (rER) and well-developed Golgi apparati were prominent in these cells. In comparison, the mitochondria were often swollen and appeared larger than those observed in the ciliated cells. The fact that no distinct secretory granules were recognizable in the nonciliated cells suggested that the present culture medium did not favorably support the secretory synthesis (Fig 2B). Occasional lysosomal granules were observed in these cells.

The basal cells were clearly recognizable in the explants. The connective tissue cells, macrophages, capillary epithelium, and nerve fibers were well preserved.

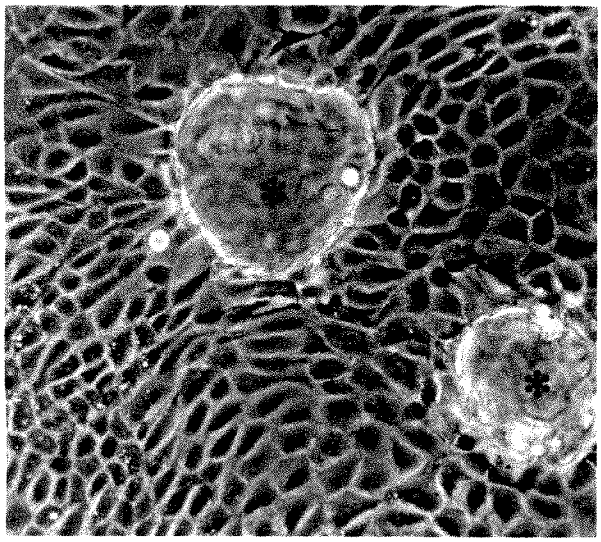

Fig 4. Light micrograph of explant, showing "dome" formations (asterisks) after 13 days in culture (original x200).

Outgrowth. Epithelial cells outgrew at the edge of the explants, forming a monolayer. The success rate of explant outgrowth depended largely on the site of the donor tissue. The highest success rate (80% to 88%) was obtained from the inferior bulla and near the orifice of the tube, in comparison to the superior bulla, which yielded outgrowth in only 23% of the explants. The shape of the cells of the outgrowth varied from hexagonal to elongated, as these cells made the transition from cuboidal to simple squamous cells (Fig 3). The cells in the growth edge showed an elongated shape.

Dividing cells, characterized by double nuclei, were generally larger than small differentiated cells with hexagonal shapes (Fig 3C). A cluster of small cobblestone-shaped cells was intermixed with a cluster of larger epithelial cells with double nuclei (Fig 3C). These larger cells appeared to be dividing or newly divided cells. The advancing edge of the outgrowth often showed an elongated cell shape oriented parallel to the explant edge. Cells at the advancing edge frequently showed ruffles. Some cells appeared giant, with multiple nuclei, even though they formed tight junctions with neighboring cells (Fig 3D). When the outgrowth became confluent, the majority of the epithelial cells attained a cobblestone appearance (Fig 3C). The cobblestone-shaped sheet of epithelium often showed a "dome" formation, produced by a fluid cavity between the epithelial monolayer of the outgrowth and the Petri dish (Fig 4).

The morphologic characteristics of the outgrowth were similar to those seen in the single squamous type of middle ear epithelium found in the bulla (Figs 5 and 6A). The single squamous cell in the outgrowth contained large ovoid nuclei, mitochondria, rER, numerous ribosomes, and Golgi apparatus. Fine cytoplasmic filaments, particularly in the base of the cells, were also observed (Fig 5C). Well-developed tight junctions were seen between cells, and tonofilaments were attached to these tight junctions. Occasionally, small clear vacuoles together with lysosomal granules were also observed. Occasionally, primary (solitary) cilia were observed in some cells but not in others (Fig 1B). Identification of primary cilia was largely made by the SEM observation and a few TEM observations. The cells with a primary cilium were randomly distributed, and no distinct pattern could be found. We were not able to correlate the glycogen contents, as determined by PAS staining, to the presence of the primary cilia as observed under light microscopy by using surface preparation.

We made an attempt to document cell size in the outgrowth (Fig 7). Although outgrowth was found on the 3rd day of explant, the size of the cells was small. Cell size began to increase until the 7th day in culture, after which it maintained a plateau until the 10th day. After that the size decreased until the 14th day. The average cell surface area of large cells was 1,440 ± 545 μm^2 (mean ± SD) on the 7th day, and the average cell surface area of small cells was 587 ± 202 μm^2 (mean ± SD) on the 3rd day.

The ciliated cells were occasionally observed migrating from the explant (Figs 5A,B and 6B), and the cilia were actively beating when observed fresh under a phase-contrast microscope. The cilia length of the ciliated cells of the outgrowth was the same as that of the explant, which was about 3.4 μm. The ciliated cells in the outgrowth generally assumed an elongated shape (Figs 3B and 6B), with their long axes oriented perpendicular to the edge of the explant (Fig 3B).

Ciliated cell migration was evident for up to 10 days after explantation from both the tympanic orifice of the eustachian tube and the inferior bulla. On the 14th day, only four of eight explants remained on the Petri dishes, and the average distance of the ciliated cell migration in those specimens was 0.69 ± 0.44 mm (mean ± SD). Ciliated cells were found within 1 mm of the explant until the 14th day. The number of ciliated cells in the outgrowth is shown in Fig 8. The number increased or remained stationary between the 4th and 7th days in culture, but it quickly declined toward the 10th day. The average number (percentage) of ciliated cells present in four specimens of which explants were maintained until the 14th day was 3.3% ± 2.9% (mean ± SD). There was a greater number of ciliated cells in the outgrowths from the tubal orifice explants than in those obtained from the inferior bulla ($p < .05$). On the 4th and 10th days there was no significant difference in the number of ciliated cells between the two outgrowth groups: one obtained from the tubal orifice and the other obtained from the inferior bulla.

The number of microvilli in different epithelial

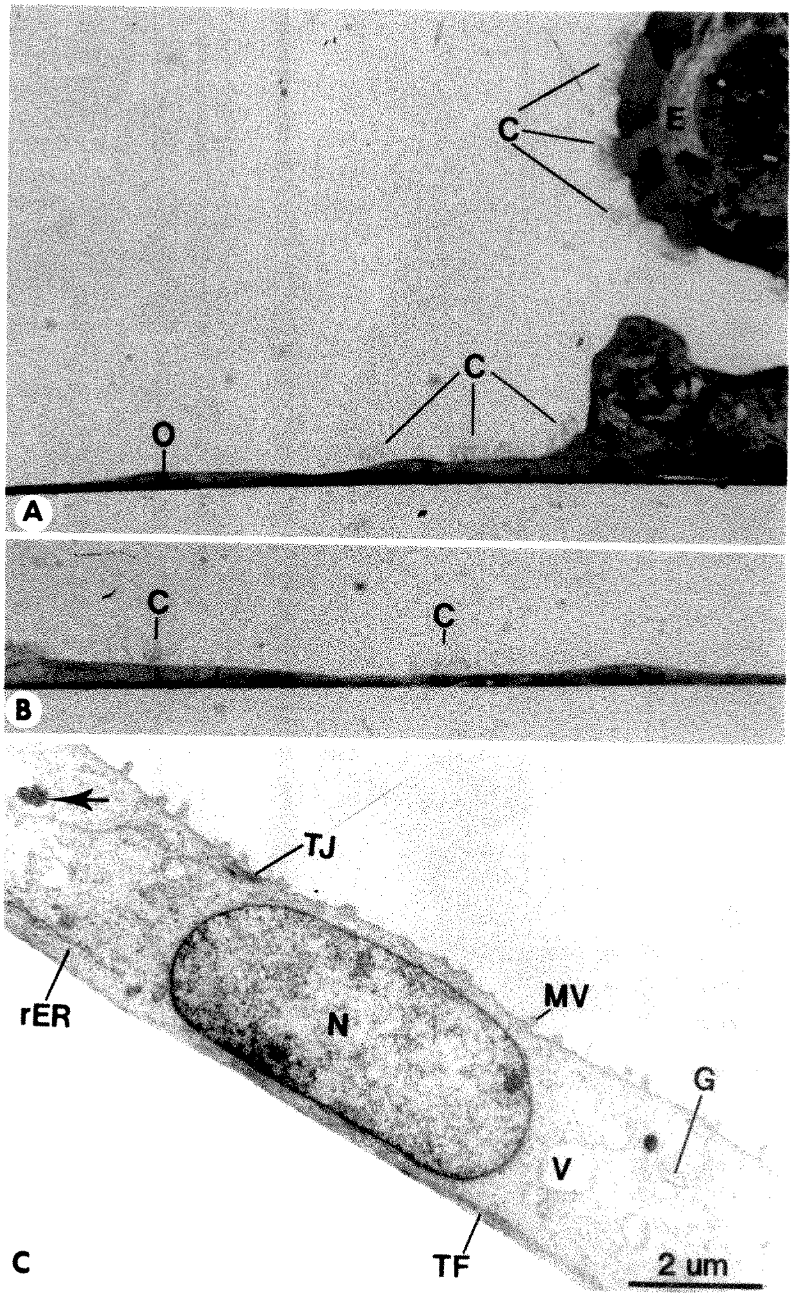

Fig 5. A) Light micrograph of Epon-embedded and thick-sectioned explant (E) and outgrowth (O), showing ciliated cells (C), after 4 days in culture (toluidine blue, original x400). B) Same specimen as A, but with distant area of outgrowth showing ciliated cells (C). C) Transmission electron micrograph of outgrowth, showing simple squamous cell with large nucleus (N), rough endoplasmic reticulum (rER), Golgi apparatus (G), vesicles (V) of various sizes, and microvilli (MV). Well-developed tight junctions (TJ) with neighboring cells and tonofilaments (TF) are clearly seen. Lysosomal granule (arrow) is frequently observed.

cells varied considerably. The microvilli of the nonciliated cells on the outgrowth were 0.5 to 0.8 μm in length — a length comparable to those of the explants (about 0.2 to 1 μm). Microvilli of ciliated cells in the outgrowth were about 3.5 μm in length, in comparison to those of the explant, which were about 2.7 μm in length.

In a few preparations, a small group of fusiform fibroblastlike cells also migrated from the edge of the explants. When observed, these cells are strikingly different from spindle-shaped epithelial cells. These cells appear long and slender, with fine-pointed ends, and often form bundles of cells distinct from even the spindle-shaped fibroblasts. Detailed illustration will be given in a succeeding paper (Nakamura et al, unpublished data). In a few cases with overt fibroblast contamination, the preparations were discarded.

Histochemistry. The original intent of PAS-AB staining was to detect secretory cells. The PAS-positive granules were stained magenta and the AB-positive granules were stained blue. The cells containing PAS- and AB-positive cytoplasmic granules appeared in various sizes in a cluster (Fig 9). In order to better understand the cellular mechanism involved in the physiology and pathophysiology of the normal middle ear mucosa and in otitis media on a cellular and molecular level, we have attempted to serially culture the chinchilla middle ear epithelium by using a number of different culture methods. The number of PAS-positive cells of the inferior bulla specimens increased up to the 10th day and

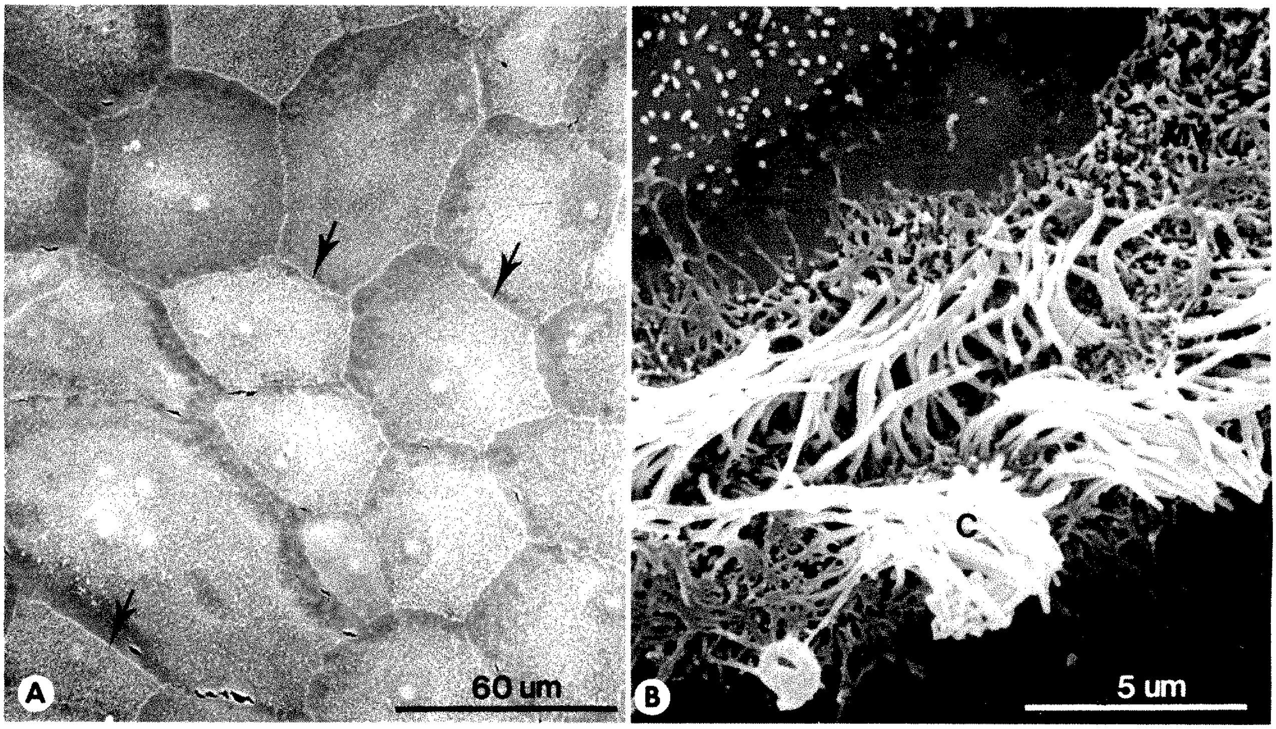

Fig 6. Scanning electron micrographs of outgrowth. A) Showing hexagonal epithelial cells of various sizes, which formed tight junctions (arrows) after 10 days in culture (original x500). B) Showing elongated ciliated cells (C) after 10 days in culture (original x600). Elongated cell shape is typical of ciliated cells in outgrowth. Tall and numerous microvilli (MV) are characteristic of these ciliated cells.

then decreased until the 14th day, at which time the number of PAS-positive cells was 21% ±5.48% (mean ± SD). On the other hand, the PAS-positive cells in the tympanic orifice-derived outgrowth increased up to the 7th day and decreased toward the 14th day, at which time the number of PAS-positive cells was 23% ±5.6% (mean ± SD). There was no significant difference between the two portions on each evaluation day. The percentage of AB-positive cells decreased on the 7th day but increased up to the 10th day.

DISCUSSION

In the present study, the technique developed by van Blitterswijk et al[2] for serial culture of the rat middle ear epithelium was successfully applied to culture chinchilla middle ear epithelium. The present culture technique successfully maintained the explant for up to 14 days in the majority of cases; this finding opens up the possibility for the present technique to be easily adapted to a number of in vitro studies.

According to our earlier study,[7] the epithelium near the tubal orifice and inferior bulla from which we obtained explants is largely cuboidal or columnar cells with complements of ciliated, secretory, and basal cells. In contrast, the epithelial cells from the superior bulla are mainly made up of simple squamous epithelium without ciliated or secretory cells and with few basal cells. Even though it is not clear why the success rate of the explants from the superior bulla was low, it can be speculated that the tall columnar or cuboidal cells with a large number of basal cells are better candidates for successful cell outgrowth.

In the present study, we were not able to determine with certainty whether the outgrowth was the result of the migration of epithelial cells from the explant or the migration of the basal cell, which became differentiated to the epithelial cell, as suggested by an in vivo study by Hentzer.[8] The fact that the migrating cell near the very edge of the explant assumed a cuboidal shape may suggest that differentiated (postmitotic) epithelial cells have migrated previously. However, the fact that some cell clusters in the outgrowth are undergoing cell division indicates that there is a dedifferentiation occurring in the outgrowth. Conversely, we can also believe that the basal cells that migrated (not the postmitotic epithelial cell) may be undergoing cell division.

The occurrence of primary cilia in nonciliated cells in both explants and in some cultured cells is interesting, because it may be a marker for growth regulatory processes that control cell cycle progression.[9] However, the presence of a primary cilium in diverse cells such as epithelial cells (sensory, dermal, and mucosal), fibroblasts, endothelial cells,[10,11] melanocytes, pericytes, and histocytes[12] in both mature and immature cells may indicate diverse functions; and its functions are yet to be determined. In the present study, we were not able to demonstrate

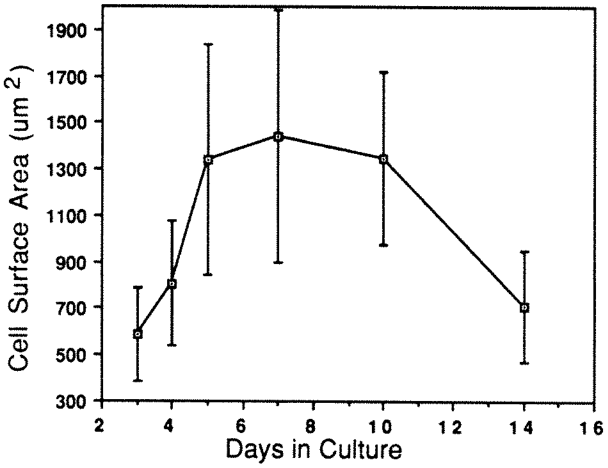

Fig 7. Averaged cell surface areas (mean ± SD) of 100 cells of outgrowth were measured at different days in culture on 35-mm Petri dish. Cell size increased up to day 5 and maintained plateau until day 10, after which cell size decreased.

its role in cell proliferation. Further systematic study is needed to clarify the role of this interesting organelle.

The size of the apical surface of the cells showed considerable variance during the cell cultivation. Small cells clustered and intermixed with clusters of large cells. The larger cells are interpreted as newly divided cells, whereas the smaller cells with a hexagonal cell surface are interpreted to be older differentiated cells. A cluster of small and large cells occurs randomly, irrespective of the distance from the explant. In the present material, the mitotic activity must occur in clusters in different parts of the outgrowth, although distant parts tend to have more mitotic activity — a finding indicating active proliferation of the cells. This observation is consistent with the data obtained by ^{3}H-thymidine labeling of human bronchial epithelial cells, which showed more radiolabeling among distant cells than those proximal to the explant.[13]

The origin of the multinucleated giant cells in the present cell culture is unclear, but they may represent cell fusion. It is possible that these may also be dividing cells. Further study is needed to document the origin and fate of these giant cells.

Our research finds that the cobblestone appearance of epithelial cells is the result of the establishment of tight junctions with neighboring cells, as shown in cultured Chinese hamster ovary cells.[14] Lechner et al[15,16] found that calcium, EGF, and serum in the culture media modulated the number of tonofilaments and desmosomal junctions. We find that these factors contribute to the terminal differentiation of the epithelial cells, as the present cobblestone formation of the middle ear epithelial cells requires calcium and EGF.

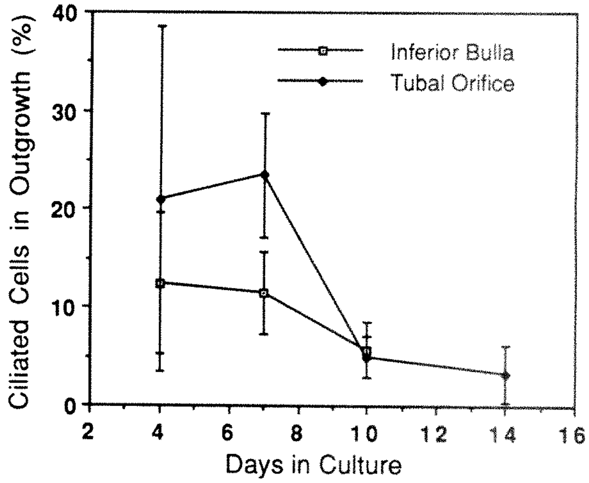

Fig 8. Number of ciliated cells migrating from explants (four each from tubal orifice and inferior bulla, respectively) was expressed as percentage of total cells counted. On 4th and 7th days, there was greater number of ciliated cells in outgrowth from explants obtained from tubal orifice than those obtained from inferior bulla ($p < .05$). Number of ciliated cells declined by 10th day. Bars — standard deviations.

The dome formation observed in the outgrowth monolayer in the present study indicates that the monolayer is formed of functioning polarized epithelial cells. This dome formation has also been observed in the Madin-Darby canine kidney cell line (which originated from the distal tubule or the collecting duct of the kidney) and the LLC-pk1 cell line (which originated from the proximal tubule of the kidney), which are both involved in ion and water transport.[17]

The cilia of the ciliated cells on the explant were identical in size to those of the ciliated cells on the outgrowth. Furthermore, there were considerable variations of microvilli occurrence on the epithelial cell surface in terms of their numbers, distribution,

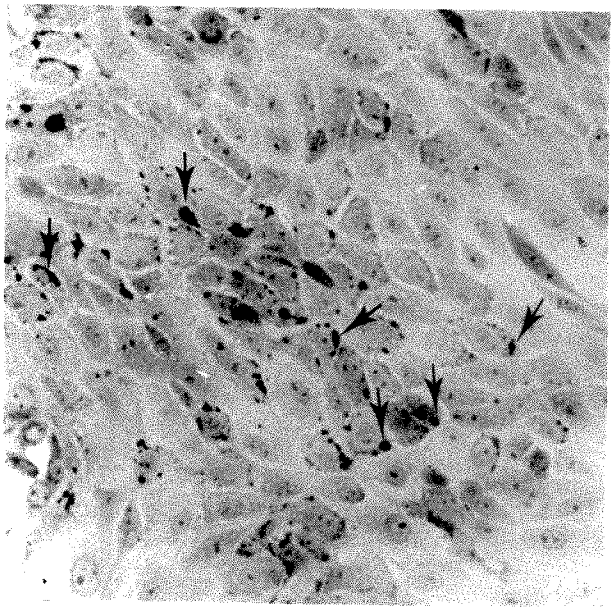

Fig 9. Light micrograph of outgrowth, showing cultured cell with periodic acid-Schiff-positive granules (arrows) of various sizes, which appear in clusters (diastase digestion, periodic acid-Schiff, original x200).

and size. As the microvilli play an important role in cell absorption,[18] it is tempting to speculate that these various states of microvilli may represent various functional states of the cells.

Hanamure and Lim[7] reported that the density of the ciliated cells of the normal chinchilla was highest in the columnar epithelium area. In the cultured cells, the number of ciliated cells of the explants from the tympanic orifice portion (where a large number of ciliated cells are present) was significantly higher than that of the explants from the inferior bulla (where a small number of ciliated cells are present). These facts suggest that this culture system reflected in vivo distribution of the ciliated cells.

Lim et al[19] reported that the secretory cells in the normal human and guinea pig middle ear epithelia contain both acid and neutral mucopolysaccharides. As the PAS-positive cells are supposed to contain neutral mucopolysaccharides and AB-positive cells contain acid mucopolysaccharides,[20] it can be assumed that the number of secretory cells corresponds to the number of AB-positive cells. Because it was not possible to identify with certainty the secretory cells by a conventional phase-contrast light microscopic examination employed in the examination of the outgrowth, we have attempted to stain the secretory granules by PAS + AB staining, which labels acidic and neutral glycoconjugates; we were able to stain some granules in certain cells. Even though these nonciliated cells in the outgrowth may indeed be secretory cells, the absence of recognizable secretory granules on an ultrastructural level in the explants and also in the outgrowth makes the interpretation of the present data difficult. As lysosomal granules may also stain PAS-positive, we interpreted these PAS + AB–positive granules observed in the present materials to be largely lysosomal granules. This interpretation is based on the fact that the glycogen particles are presumably digested by the enzyme and the secretory granules are most likely depleted in the present materials. Thus, the present method has serious limitations for the study of secretory activity, as most of the secretory granules were depleted when maintained in the present culture medium. Further study with a modified medium to increase the synthesis of the secretory product is needed before these cultured cells can be effectively used for such a study.

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IMAGING CASE STUDY OF THE MONTH

LARYNGEAL LIPOMA

CLARA L. ORTIZ, MD ALFRED L. WEBER, MD

BOSTON, MASSACHUSETTS

Benign laryngeal lipomas are uncommon lesions and occur most often in the epiglottis and aryepiglottic folds, in which the richest subepithelial fat deposits are encountered.[1] Zakrzewski[2] reviewed the literature in 1965 and found 70 cases. Since that time only a few additional cases have been reported.[3-5] We present another case of a laryngeal lipoma and discuss its features on computed tomography (CT).

CASE REPORT

A 35-year-old man presented with an 8-month history of increasing difficulty with swallowing along with problems sleeping at night. He also complained of some respiratory problems and incidents of choking. On indirect laryngoscopic examination, fullness was noted in the right preepiglottic space, with pressure exerted on the base of the tongue and the left aryepiglottic fold. The vocal cords appeared normal, with normal mobility bilaterally. No adenopathy was found.

A CT scan was performed and revealed a right laryngeal hypodense mass consistent with fat. The lesion involved the upper left pyriform sinus with displacement of the left aryepiglottic fold medially and extralaryngeal extension superiorly (see Figure).

Four days later, owing to the patient's symptoms, surgical excision was performed with a transverse skin incision. A 5 x 6-cm well-encapsulated lesion was found, located mostly in the upper preepiglottic space. The superior aspect of the tumor was just inferior to the hyoid bone, and the inferior aspect of the lesion was deep to the upper thyroid lamina bilaterally. The superior laryngeal nerve was preserved bilaterally. The pathologic diagnosis was benign lipoma.

DISCUSSION

Lipomas occur predominantly in men, with a male to female ratio of 5 to 1, and are found most often in the sixth and seventh decades.[1] About 13% of lipomas are located in the head and neck, most of which are found in the posterior neck. They are noted less frequently in the anterior neck, temporal fossa, oral cavity, pharynx, larynx, and parotid gland.[5,6]

A lipoma is a slow-growing tumor that usually evolves over a period of many years[7] and is often asymptomatic. In the larynx, the most common presenting symptoms are an intraluminal mass that encroaches upon the airway.[1,4] In addition, the feeling of a lump in the throat, hoarseness, dysphagia, and/or respiratory difficulties, especially if the tumor is pedunculated and creates a "ball-valve" effect, are other complaints. Lipomas of the larynx may also occur in individuals with numerous lipomas located at other body sites.

There are several types of lipomatous tumors that have been differentiated histologically. With the introduction of CT and magnetic resonance imaging it has been possible to diagnose and characterize these lesions and to differentiate them from many other types of tumor. Computed tomography allows accurate localization and definition of the extension prior to surgical removal.

The CT appearance of a lipoma is that of a homogeneous, low-attenuation mass that usually measures between −65 and −125 Hounsfield units. There is no clearly defined capsule, but the lesion is well delineated from the surrounding soft tissue. Occasionally, a marginal microscopic infiltration can appear, accounting for recurrent lipomas.

When there is infiltration of adjacent muscles, a liposarcoma should be suspected. Liposarcomas are characterized by varying degrees of differentiation and display myxomatous features, cellular pleomorphism, and hyperchromatic and mitotic nuclei. These tumors are extremely rare in the head and neck. Well-differentiated liposarcomas have a high propensity for local recurrence and rarely metastasize, while the poorly differentiated variety metastasize more frequently and have a less favorable prognosis.

Liposarcomas are thought to arise de novo, but a few cases of malignant degeneration of benign lipomas have been reported.[7] Computed tomography demonstrates a heterogeneous mass that is slightly denser than an ordinary lipoma.

Angiomatous features are seen in 5% to 17% of all lipomas. Angiolipomas are benign tumors composed of lipocytes with vascular proliferation. An-

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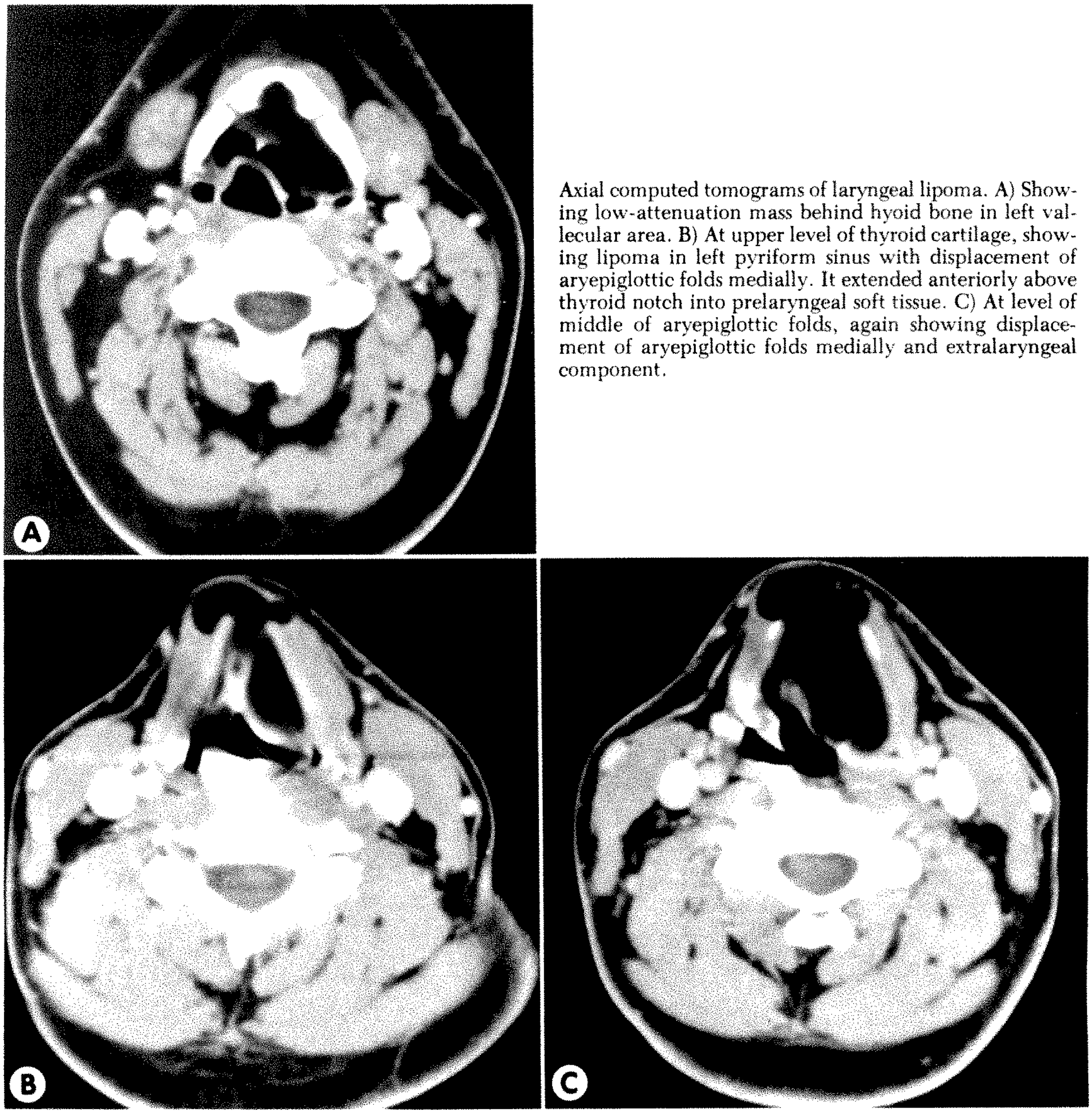
From the Department of Radiology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

REPRINTS — Alfred L. Weber, MD, Dept of Radiology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.



Axial computed tomograms of laryngeal lipoma. A) Showing low-attenuation mass behind hyoid bone in left vallecular area. B) At upper level of thyroid cartilage, showing lipoma in left pyriform sinus with displacement of aryepiglottic folds medially. It extended anteriorly above thyroid notch into prelaryngeal soft tissue. C) At level of middle of aryepiglottic folds, again showing displacement of aryepiglottic folds medially and extralaryngeal component.

giolipomas may resemble the large-vessel type of hemangiomas in skeletal muscle, and therefore they will partially enhance on contrast CT.[8]

If the lipoma is mixed with fibrous tissue instead of vessel, it is referred to as a fibrolipoma. On CT, the low-attenuation lipomatous tissue is traversed by higher-density fibrous strands.

When clinical symptoms are present, the treatment of choice is total excision. Since most of these neoplasms are located high in the supraglottic region, endoscopic removal is often feasible for smaller lesions.

The differential diagnosis includes benign tumors, such as neurofibroma, leiomyoma, chondroma, papilloma, cystic hygroma, and parenchymal cyst. However, none of these lesions have the attenuation values of a lipoma.

In this case of a benign lipoma of the larynx, the patient's clinical symptoms warranted surgical intervention. We report this case because of the rare location of the lipoma and to emphasize the ability of CT to determine the diagnosis.

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PATHOLOGY CONSULTATION

BASALOID SALIVARY CARCINOMA

JOHN G. BATSAKIS, MD MARIO A. LUNA, MD

HOUSTON, TEXAS

The basaloid salivary carcinoma is proposed as the malignant counterpart of the basal cell or basaloid monomorphic adenoma. The carcinoma can arise de novo or by evolution from a maternal monomorphic adenoma. Particularly at risk for the latter sequence is the dermal analogue monomorphic adenoma. Preponderantly a parotid gland neoplasm, the basaloid carcinoma appears to be a biologically low-grade carcinoma with a low mortality but with a respectable local aggressiveness and recurrence rate.

It is likely there will always be a number of benign or malignant salivary gland tumors that cannot be readily placed in any accepted taxonomic scheme. Such tumors are usually listed at the end of surveys under categories such as unclassified, unclassifiable, or atypical variants of otherwise classified salivary gland tumors. Within such listings are tumors that exhibit a range of biologic behavior from clinically benign to high-grade malignancy. Following repeated recognition of cytoarchitectural patterns and collections of similar cases with clinicopathologic correlations, some members of the unclassified or atypical variant groups secure their own niche in classifications of salivary gland neoplasia. The emergence of monomorphic adenomas is representative of such a process.[1-3]

In like manner, two recent studies entailing 37 cases have presented data (see Table[4,5]) that may serve to move a salivary gland carcinoma from an "unclassified" status to the malignant counterpart of the basal cell or basaloid monomorphic adenomas. Suspected, yet largely undefined, these malignant neoplasms have been called atypical variants of monomorphic adenomas, basal cell adenocarcinomas, malignant basaloid tumors, hybrid monomorphic adenomas, carcinomas ex monomorphic adenoma, or basaloid salivary carcinomas. There are nosologic limitations to each of these terms, but each conveys a histologic similarity or evolution from a coexisting monomorphic adenoma of the basal or basaloid type.

There is no histogenetic preclusion to a carcinoma arising in a monomorphic adenoma, and carcinoma ex pleomorphic adenoma, malignant oncocytoma, and malignant Warthin's tumor certainly serve as precedents for the event. In that light, Luna et al[4] *required* the histopathologic identification of a coexisting basaloid monomorphic adenoma for their carcinomas ex monomorphic adenoma. Ellis and Wiscovitch[5] excluded such mixed pattern tumors, but their selections had to have cytomorphologic features of monomorphic (basal) adenomas. Given the histologic similarities and the clinicopathologic features of the tumors described by Luna et al[4] and Ellis and Wiscovitch,[5] it appears that basaloid salivary carcinomas can evolve de novo or from a monomorphic adenoma.

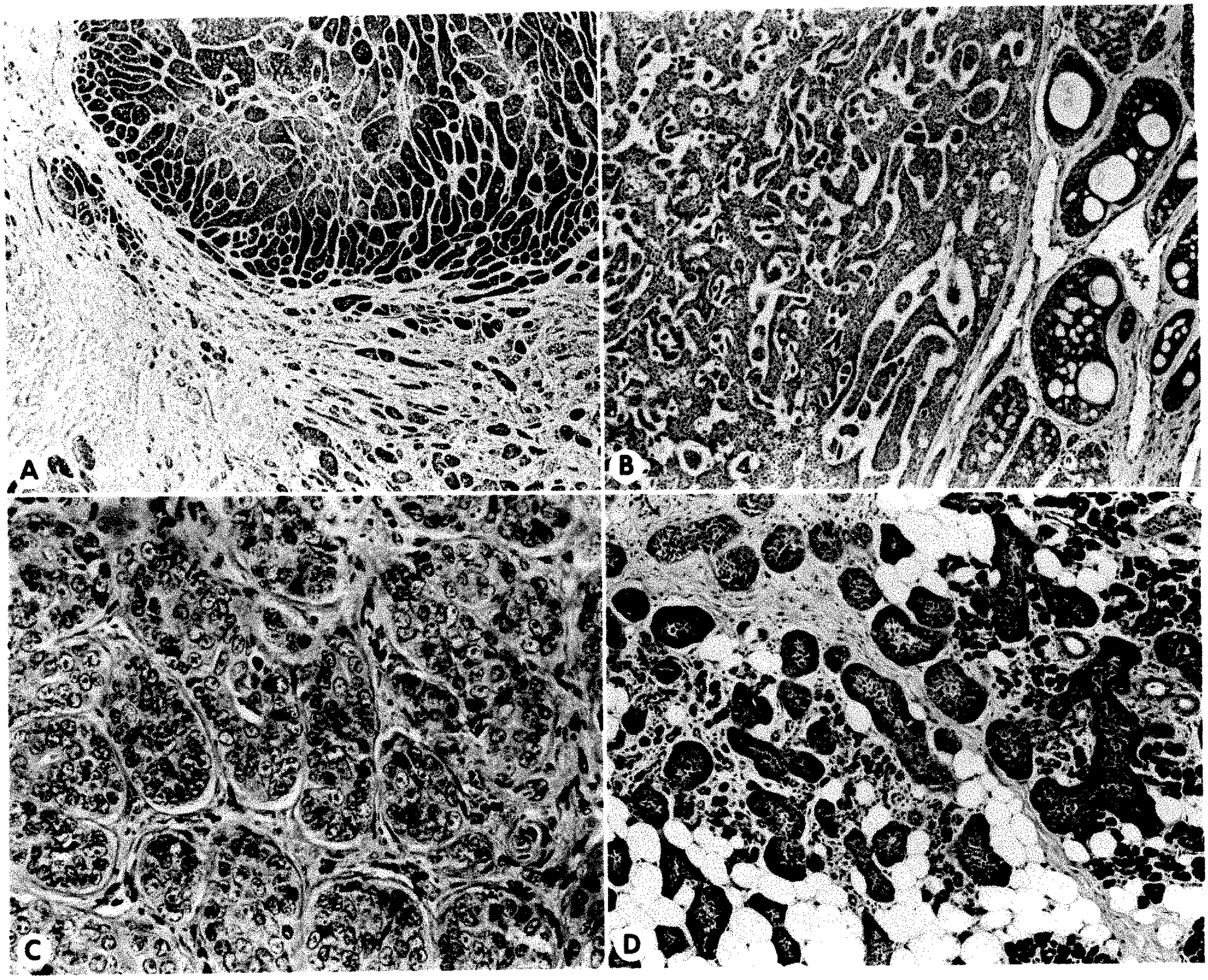
To date, basaloid carcinomas have been almost exclusively major salivary (preponderantly parotid) gland in origin. A salivary gland–skin adnexal (dermal cylindroma, eccrine spiradenoma, trichoepithelioma) diathesis[6,7] has been found in 10.8% of the patients. This association is not seen with any other salivary gland carcinoma, but is known to exist with the dermal analogue monomorphic adenomas of major salivary glands.[4,6,7] As declared by follow-up periods, the carcinomas appear to be bio-

BASALOID CARCINOMAS OF SALIVARY GLANDS

Clinicopathologic Features	*Luna et al[4] (n = 8)*	*Ellis and Wiscovitch[5] (n = 29)*
Age and sex of patients	55 to 79 y (mean, 68.3); 4 men, 4 women	27 to 92 y (mean, 58); 16 men, 12 women, 1 unspecified
Salivary gland site	6 parotid; 1 submandibular; 1 palate	26 parotid or presumed parotid; 3 submandibular
Size of tumor	3.0 to 7.0 cm (mean, 3.7)	0.7 to 4.0 cm (mean, 2.1)
"Maternal" monomorphic adenoma identified	8	0
Salivary-skin adnexal diathesis	1	3
Recurrences	6 (1 to 4 times)	7/25 traceable cases 1 to 2 times
Metastases	0	3 to regional lymph nodes; 1 of these to lungs
Mortality	0 (2 to 16 y follow-up)	1 (6 mo to 10.3 y follow-up)

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.



Basaloid salivary carcinoma. A) Basaloid adenocarcinoma of parotid gland (H & E, original x25). Except for invasive basaloid ducts in connective tissue, this carcinoma has strong histologic similarity to dermal analogue monomorphic adenoma. B) Hybrid monomorphic adenoma of parotid gland with adenoid cystic carcinoma histomorphology on right in apposition to trabecular basaloid monomorphic adenoma on left (H & E, original x65). C) Basaloid adenocarcinoma of parotid gland (H & E, original x200). Neoplastic cells are arranged in solid nests in which early lumen formation is seen. D) Parotid gland parenchyma is invaded by basaloid nests of carcinoma (H & E, original x110).

logically low grade. Recurrence rates approximate 28%, with the differences noted between the two series in the Table perhaps attributable to the larger sizes and multifocality of the tumors, as well as closer follow-up, described by Luna et al.[4]

Ellis and Gnepp,[8] in a discussion of "basal cell adenocarcinomas" of salivary glands, have remarked on the "marked similarities to basal cell adenomas, especially the membraneous (dermal analogue) type." This allusion is strengthened by noting that 11 of the 37 (29.7%) accumulated cases of basaloid salivary carcinoma either arose from a dermal analogue type of monomorphic adenoma or were subclassified as membranous carcinomas. Even in Ellis and Wiscovitch's[5] solid basal cell adenocarcinomas, an eosinophilic hyaline material was often present within the epithelial nests. These findings empirically suggest that the dermal analogue (membranous) adenoma is at the highest risk for spawning a basaloid salivary carcinoma.[4]

The light optic criteria for a basaloid salivary carcinoma are either a marked similarity to basal cell or basaloid monomorphic adenoma (see Figure, A) or coexistence of the carcinoma with such a monomorphic adenoma (see Figure, B). There may be only minimal deviation of the carcinoma's cytoarchitecture from that of a basal cell or basaloid monomorphic adenoma, or the carcinoma shows all of the accepted stigmata of an epithelial malignancy: prominent mitotic activity, loss of cellular polarity with pleomorphic and polymorphic cells (see Figure, C), coagulative necrosis, and invasion of nerves and lymph-vascular spaces. Regardless of the cytomorphologic aberrations, a destructive infiltrative growth pattern by a solid, tubuloductal, or trabecular neoplasm is always evident (see Figure, D).

Differential diagnosis obviously includes the basal cell or basaloid monomorphic adenoma and other neoplasms with a basaloid cell population, ie, adenoid cystic carcinoma and metastatic cutaneous basal cell carcinoma.

The invasive properties of a basaloid salivary carcinoma exclude monomorphic adenoma. Low-grade adenoid cystic carcinomas usually have a prominent myoepithelial component around the ductal elements. They and the other grades of adenoid cystic carcinomas (cribriform or cylindromatous and solid) are rarely "pure," so that their specific features serve as differential diagnostic criteria. Historical or clinical evidence of a cutaneous adnexal or basal cell carcinoma in the region of the involved major salivary gland should persuade the pathologist away from a basaloid salivary carcinoma diagnosis.

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LETTERS TO THE EDITOR

To the Editor:

I read with great interest the case report "Inner Ear Decompression Sickness Combined With a Fistula of the Round Window" (*Ann Otol Rhinol Laryngol* 1990;99:733-7) by G. H. Adkisson and A. P. d'E. Meredith. I believe that this article may be misleading in two basic points concerning the evaluation and treatment of diving-related inner ear injuries.

The first point is that in the case presented, the vestibular system was evaluated only by physical examination. Neither primary nor follow-up laboratory vestibular examinations were carried out, although the patient had presented himself with the symptoms of "dizziness," nausea, and loss of balance in addition to his other symptoms.

Animal studies and clinical data, including our own experience, have shown that vestibular damage can occur alone or in combination with the cochlear damage caused by inner ear barotrauma[1-3] or decompression sickness.[4-8] In addition, the primary decompression vestibular insult may initiate slowly developing histopathologic changes that might be completed only many months later, as demonstrated in the squirrel monkey inner ear decompression sickness model[4] and a postmortem case report.[5] Symptoms of vestibular involvement are usually masked in everyday activities by central vestibular compensatory mechanisms[9]; thus, vestibular damage may be diagnosed only by specific tests such as electronystagmography and/or rotatory chair examination. When diving-related inner ear damage is suspected, the patient's vestibular system and not only cochlear functions should be thoroughly examined. This is a critical point taking into account that underwater, visual and proprioceptive inputs to the central nervous system are often missing, and existing undiagnosed vestibular damage may jeopardize the diver's spatial orientation and lead to life-threatening situations.

The second point is that recompression should generally be avoided in the event of inner ear barotrauma. Inner ear barotrauma is directly related to inadequate middle ear pressure equalization during the descent phase of diving, leading by the explosion or implosion mechanism to intralabyrinthine membrane breakdown and/or perilymphatic fistula.[10] Under these conditions of failed middle ear pressure equalization ability, recompression repeats the pathogenetic chain of events. This might expose the inner ear to recurrent barotrauma, aggravating the initial vestibulocochlear damage.[11] When recompression therapy is a must, insertion of ventilation tubes is a simple method of eliminating this risk. In the case reported, although the possibility of inner ear barotrauma was raised, no measures were taken to prevent the risk of recurrent inner ear barotrauma prior to the commencement of recompression therapy.

Avi Shupak, MD
Carmel Lady Davis Hospital
Haifa 34362, Israel

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To the Editor:

Dr Shupak's comments are appreciated and serve to highlight the concepts presented in our paper. Diving casualties often require immediate recompression to minimize damage and obtain the most complete resolution of symptoms. Time is of the essence, and the clinician must rely on simple physical examination to diagnose and treat such injuries. This diver conducted an evening dive and was referred to us, markedly symptomatic, in the middle of the night. Our recompression facility, like most military chambers, was not located near our support hospital. A differential diagnosis was carefully considered and included inner ear decompression sickness (DCS) and barotrauma. The most serious, potentially debilitating injury had to be treated promptly. Any delay in the treatment of DCS reduces the chance of a successful outcome. This is particularly true in the case of inner ear DCS where, as Dr Shupak correctly indicates, ongoing damage may be occurring. Delaying treatment to obtain information that may or may not support a secondary diagnosis is unacceptable in such a situation.

Electronystagmography, as in all functional tests of hearing or labyrinthine reaction, is used along with history and physical examination as an aid and is rarely diagnostic by itself. Central vestibular compensatory mechanisms take time to develop and would not mask early vestibular symptoms. An otolaryngologic evaluation elicited clear symptoms of a round window rupture, and surgical intervention resulted in an asymptomatic patient. The use of electronystagmography prior to recompression was clearly inappropriate, as it would have delayed treatment and could have resulted in further damage. Electronystagmography is of questionable value in an asymptomatic patient and would not have altered our management.

Recompression where the diagnosis between inner ear DCS and barotrauma is in doubt is an accepted procedure. Recompression has been conducted on divers in whom the diagnosis of barotrauma was later confirmed,[1] and there was no worsening in their symptoms or, more importantly, in their eventual outcome. Insertion of ventilation tubes in not routine in such situations. Their placement is not without risk, and the potential of inducing further barotrauma may be avoided by the use of a slow, carefully controlled recompression. In the rare instance in which equalization remains a problem, a simple myringotomy may be more appropriate.

G. H. Adkisson, MD
Department of Anesthesiology
Naval Hospital San Diego
San Diego, CA 92134

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FOR THE RECORD

At least three views exist about the cause of Spastic Dysphonia: physicians believe the cause is medical; psychiatrists believe it is psychological; and my position as a voice and speech pathologist is that Spastic Dysphonia is caused by misuse and abuse of the speaking voice. It is a mechanical problem, with psychological overtones. The individual is figuratively talking with the brakes on, squeezing the voice from the lower throat, and the breathing is in the wrong gear.

In 1980 in the Proceedings of the 18th Congress of the International Association of Logopedics and Phoniatrics, I reported on nine patients who had recovered from Spastic Dysphonia by Direct Voice Rehabilitation and five patients who were recovering. One patient, Dr. Don Dodson, who discussed his voice problem at this meeting, fully recovered his voice the next year. But Herbert Dedo, M.D., in the April 1991 issue of the Annals of Otology, Rhinology & Laryngology, writes: "Regarding need, many otolaryngologists, voice therapists, neurologists, and psychiatrists, after correctly diagnosing a case of SD, still are unaware that it is not curable (ie, spasticity is not eliminated) with voice therapy . . ." (pg. 277).

In 1982, at Cedars-Sinai Medical Hospital, Los Angeles, I presented three patients who had confirmed severe Spastic Dysphonia to an audience of Ear, Nose, and Throat doctors. These patients told the audience how they had recovered their speaking voices by Direct Voice Rehabilitation. But Herbert Dedo, M.D., in the above mentioned journal writes: "The only effective treatment at the present time is paralysis of one vocal cord temporarily with botulin injection or permanently with left RLN section . . . " (pg. 278).

In 1990, I was again invited to return as guest speaker at Cedars-Sinai Medical Center. This time I presented five patients with diagnosed Spastic Dysphonia and discussed how I had helped them with Direct Voice Rehabilitation. Regarding the treatment of Spastic Dysphonia by Direct Voice Rehabilitation in patients seen in his private practice group, a very prominent otolaryngologist, Edward A. Kantor, M.D., Chairman, Division of Otolaryngology, Head and Neck Surgery, Cedars-Sinai Medical Center, Los Angeles, has this to say: "Dr. Morton Cooper has shown unusual expertise in treating patients with Spastic Dysphonia. His methods of voice therapy in our patients afflicted with this markedly disabling disease have been highly successful."

Over the past fifteen years, I have been to meetings of the American Speech-Language-Hearing Association, the California Speech-Language-Hearing Association, and the International Association of Logopedics and Phoniatrics, presenting with tapes or with actual patients the recovery from Spastic Dysphonia by Direct Voice Rehabilitation. In articles and videos (in local TV shows on American Cable and Century Cable. I have reported on 'before' and 'after' patients who have had Spastic Dysphonia.

The late Henry Fonda had Spastic Dysphonia. Through a program of Direct Voice Rehabilitation, Mr. Fonda was able to recover his voice and film "On Golden Pond," a movie for which he received an Oscar. Another patient, Dr. Don Dodson said in a Los Angeles Times interview that he had fully recovered from Spastic Dysphonia. Zelda Pollock, who developed Spastic Dysphonia while teaching, went on KCBS to tell about her recovery.

People come from all over the world for my help in resolving Spastic Dysphonia. A professor came from the Middle East, having been directed by a medical doctor in the United States, on an RX form, to "chew on a golf ball." By Direct Voice Rehabilitation, the patient recovered in a year. I have received yearly reports from him; he has retained a normal voice for the past fifteen years. Jim Johnson, a minister from the Mid-West, having had severe Spastic Dysphonia for almost nine years and trying all kinds of therapy unsuccessfully (even going to the Mayo Clinic), is now talking with a normal voice; he underwent an intensive daily one month program of Direct Voice Rehabilitation with me. He says his voice recovery is a miracle; his voice remains excellent after five years.

I have found that Spastic Dysphonia, which I call the monster voice, isn't hopeless and that it has had an excellent prognosis in my office. My techniques differ from those of my colleagues, and I am sharply critical of what some of my colleagues and medical associates do for Spastic Dysphonia. Patients with Spastic Dysphonia are usually not given options to surgery and botulin injection. The downside of these procedures, I find, is not presented to these patients. Direct Voice Rehabilitation is a holistic, conservative, non-risk, non-invasive and natural way of helping those with Spastic Dysphonia and patients should be given this as an alternative approach. Are the medical doctors and the speech pathology associations playing the politics of voice?

In 1973 in my textbook, Modern Techniques of Vocal Rehabilitation, I wrote about recovery from Spastic Dysphonia. In my two most recent books, Change Your Voice, Change Your Life and Winning With Your Voice, I discuss the way to get a better, more effective voice, and I detail how those suffering from Spastic Dysphonia have been helped by my Direct Voice Rehabilitation program.

If you or your organization wish to hear my approach to Spastic Dysphonia, please write, 10921 Wilshire Blvd., Ste. 401, Los Angeles, CA 90024 or call 1-800-932-3221.

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